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CB 1/CB 2 RECEPTOR LIGANDS AND THEIR USE IN THE TREATMENT OF PAIN

Abstract:

Abstract of WO2004060882

Compounds of formula (I) or pharmaceutically acceptable salts thereof wherein Ar 1<, Ar 2?, R 1?, R 2?, n and X are as defined in the specificationas well as salts and pharmaceutical compositions i e8d ncluding the compounds are prepared. They are useful in therapy, in particular in the management of pain. Data supplied from the esp@cenet database - Worldwide

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(71) Applicant *(for all designated States except US)*: **ASTRAZENECA AB** [SE/SE]; S-151 85 Södertälje (SE).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: **LEUNG, Carmen** [CA/CA]; AstraZeneca R & D Montreal, 7171 Frederick-Banting, St. Laurent, Montreal, Québec H4S 1Z9 (CA). **TOMASZEWSKI, Miroslaw** [CA/CA]; AstraZeneca R & D Montreal, 7171 Frederick-Banting, St. Laurent, Montreal, Québec H4S 1Z9 (CA). **WOO, Simon** [CA/CA]; AstraZeneca R & D Montreal, 7171 Frederick-Banting, St. Laurent, Montreal, Québec H4S 1Z9 (CA).

(74) Agent: **GLOBAL INTELLECTUAL PROPERTY**; AstraZeneca AB, S-151 85 Södertälje (SE).

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(54) Title: CB 1/CB 2 RECEPTOR LIGANDS AND THEIR USE IN THE TREATMENT OF PAIN

(57) Abstract: Compounds of formula (I) or pharmaceutically acceptable salts thereof wherein Ar¿1?, Ar¿2?, R¿1?, R¿2?, n and X are as defined in the specificationas well as salts and pharmaceutical compositions including the compounds are prepared. They are useful in therapy, in particular in the management of pain.

CB 1/CB 2 receptor ligands and their use in the treatment of pain.

BACKGROUND OF THE INVENTION

1. Field of the invention

The invention is related to compounds which are CB_1/CB_2 receptor ligands, pharmaceutical compositions containg these compounds, manufacturing processes thereof and uses thereof, and more particularly to compounds that are CB_1/CB_2 receptor agonists. The present invention may also relate to compounds that may be effective in treating pain, cancer, multiple sclerosis, Parkinson's disease, Huntington's chorea, Alzheimer's disease, anxiety disorders, vision and/or eye related disorders, gastrointestinal disorders and cardiavascular disorders.

2. Discussion of Relevant Technology

Pain management has been an important field of study for many years. It has been well known that cannabinoid receptor (e.g., CB_1 receptors, CB_2 receptors) ligands, especially agonists produce relief of pain in a variety of animal models by interacting with CB_1 and/or CB_2 receptors. Generally, CB_1 receptors are located predominately in the central nervous system, whereas CB_2 receptors are located primarily in the periphery and are primarily restricted to the cells and tissues derived from the immune system.

While the conventional CB_1 receptor agonists and CB_1/CB_2 receptor agonists, such as tetrahydrocannabinol (THC) and opiate drugs, are highly effective in anti-nociception models in animals, they tend to exert many undesired CNS (central nerve system) side-effects, e.g., psychoactive side effects and the abuse potential of opiate drugs.

Therefore, there is a need for new CB_1/CB_2 receptor ligands such as agonists useful in managing pain or treating other related symptoms or diseases with reduced or minimal undesirable CNS side-effects. The compounds of the invention may be used to avoid the undesired CNS side effects which arise through the central CB1 mechanism.

DISCLOSURE OF THE INVENTION

The present invention provides CB_1/CB_2 receptor ligands which are useful in treating pain and other related symptoms or diseases.

Definitions

Unless specified otherwise within this specification, the nomenclature used in this specification generally follows the examples and rules stated in *Nomenclature of Organic Chemistry, Sections A, B, C, D, E, F, and H*, Pergamon Press, Oxford, 1979, which is incorporated by references herein for its exemplary chemical structure names and rules on naming chemical structures. Optionally, a name of a compound may be generated using a chemical naming program: ACD/ChemSketch, Version 5.09/September 2001, Advanced Chemistry Development, Inc., Toronto, Canada.

"CB_1/CB_2 receptors" means CB_1 and/or CB_2 receptors.

The term "C_{m-n}" or "C_{m-n} group" used alone or as a prefix, refers to any group having m to n carbon atoms, and having 0 to n multivalent heteroatoms selected from O, S, N and P, wherein m and n are 0 or positive integers, and n>m. For example, "C_{1-6}" would refer to a chemical group having 1 to 6 carbon atoms, and having 0 to 6 multivalent heteroatoms selected from O, S, N and P.

The term "hydrocarbon" used alone or as a suffix or prefix, refers to any structure comprising only carbon and hydrogen atoms up to 14 carbon atoms.

The term "hydrocarbon radical" or "hydrocarbyl" used alone or as a suffix or prefix, refers to any structure as a result of removing one or more hydrogens from a hydrocarbon.

The term "alkyl" used alone or as a suffix or prefix, refers to monovalent straight or branched chain hydrocarbon radicals comprising 1 to about 12 carbon atoms. Unless otherwise specified, "alkyl" general includes both saturated alkyl and unsaturated alkyl.

The term "alkylene" used alone or as suffix or prefix, refers to divalent straight or branched chain hydrocarbon radicals comprising 1 to about 12 carbon atoms, which serves to links two structures together.

The term "alkenyl" used alone or as suffix or prefix, refers to a monovalent straight or branched chain hydrocarbon radical having at least one carbon-carbon double bond and comprising at least 2 up to about 12 carbon atoms.

The term "alkynyl" used alone or as suffix or prefix, refers to a monovalent straight or branched chain hydrocarbon radical having at least one carbon-carbon triple bond and comprising at least 2 up to about 12 carbon atoms.

The term "cycloalkyl," used alone or as suffix or prefix, refers to a monovalent ring-containing hydrocarbon radical comprising at least 3 up to about 12 carbon atoms.

The term "cycloalkenyl" used alone or as suffix or prefix, refers to a monovalent ring-containing hydrocarbon radical having at least one carbon-carbon double bond and comprising at least 3 up to about 12 carbon atoms.

The term "cycloalkynyl" used alone or as suffix or prefix, refers to a monovalent ring-containing hydrocarbon radical having at least one carbon-carbon triple bond and comprising about 7 up to about 12 carbon atoms.

The term "aryl" used alone or as suffix or prefix, refers to a monovalent hydrocarbon radical having one or more polyunsaturated carbon rings having aromatic character, (*e.g.*, 4n + 2 delocalized electrons) and comprising 5 up to about 14 carbon atoms.

The term "arylene" used alone or as suffix or prefix, refers to a divalent hydrocarbon radical having one or more polyunsaturated carbon rings having aromatic character, (*e.g.*, 4n + 2 delocalized electrons) and comprising 5 up to about 14 carbon atoms, which serves to links two structures together.

The term "heterocycle" used alone or as a suffix or prefix, refers to a ring-containing structure or molecule having one or more multivalent heteroatoms, independently selected from N, O, P and S, as a part of the ring structure and including at least 3 and up to about 20 atoms in the ring(s). Heterocycle may be saturated or unsaturated, containing one or more double bonds, and heterocycle may contain more than one ring. When a heterocycle contains more than one ring, the rings may be fused or unfused. Fused rings generally refer to at least two rings share two atoms therebetween. Heterocycle may have aromatic character or may not have aromatic character.

The term "heteroalkyl" used alone or as a suffix or prefix, refers to a radical formed as a result of replacing one or more carbon atom of an alkyl with one or more heteroatoms selected from N, O, P and S.

The term "heteroaromatic" used alone or as a suffix or prefix, refers to a ring-containing structure or molecule having one or more multivalent heteroatoms, independently selected from N, O, P and S, as a part of the ring structure and including at least 3 and up to about 20 atoms in the ring(s), wherein the ring-

containing structure or molecule has an aromatic character (*e.g.*, 4n + 2 delocalized electrons).

The term "heterocyclic group," "heterocyclic moiety," "heterocyclic," or "heterocyclo" used alone or as a suffix or prefix, refers to a radical derived from a heterocycle by removing one or more hydrogens therefrom.

The term "heterocyclyl" used alone or as a suffix or prefix, refers a monovalent radical derived from a heterocycle by removing one hydrogen therefrom.

The term "heterocyclylene" used alone or as a suffix or prefix, refers to a divalent radical derived from a heterocycle by removing two hydrogens therefrom, which serves to links two structures together.

The term "heteroaryl" used alone or as a suffix or prefix, refers to a heterocyclyl having aromatic character.

The term "heterocylcoalkyl" used alone or as a suffix or prefix, refers to a heterocyclyl that does not have aromatic character.

The term "heteroarylene" used alone or as a suffix or prefix, refers to a heterocyclylene having aromatic character.

The term "heterocycloalkylene" used alone or as a suffix or prefix, refers to a heterocyclylene that does not have aromatic character.

The term "six-membered" used as prefix refers to a group having a ring that contains six ring atoms.

The term "five-membered" used as prefix refers to a group having a ring that contains five ring atoms.

A five-membered ring heteroaryl is a heteroaryl with a ring having five ring atoms wherein 1, 2 or 3 ring atoms are independently selected from N, O and S.

Exemplary five-membered ring heteroaryls are thienyl, furyl, pyrrolyl, imidazolyl, thiazolyl, oxazolyl, pyrazolyl, isothiazolyl, isoxazolyl, 1,2,3-triazolyl, tetrazolyl, 1,2,3-thiadiazolyl, 1,2,3-oxadiazolyl, 1,2,4-triazolyl, 1,2,4-thiadiazolyl, 1,2,4-oxadiazolyl, 1,3,4-triazolyl, 1,3,4-thiadiazolyl, and 1,3,4- oxadiazolyl.

A six-membered ring heteroaryl is a heteroaryl with a ring having six ring atoms wherein 1, 2 or 3 ring atoms are independently selected from N, O and S.

Exemplary six-membered ring heteroaryls are pyridyl, pyrazinyl, pyrimidinyl, triazinyl and pyridazinyl.

The term "substituted" used as a prefix refers to a structure, molecule or group, wherein one or more hydrogens are replaced with one or more C_{1-12}hydrocarbon groups, or one or more chemical groups containing one or more heteroatoms selected from N, O, S, F, Cl, Br, I, and P. Exemplary chemical groups containing one or more heteroatoms include heterocyclyl, $-NO_2$, -OR, -Cl, -Br, -I, -F, $-CF_3$, -C(=O)R, -C(=O)OH, $-NH_2$, -SH, -NHR, $-NR_2$, -SR, $-SO_3H$, $-SO_2R$, -S(=O)R, -CN, -OH, -C(=O)OR, $-C(=O)NR_2$, -NRC(=O)R, oxo (=O), imino (=NR), thio (=S), and oximino (=N-OR), wherein each "R" is a C_{1-12}hydrocarbyl. For example, substituted phenyl may refer to nitrophenyl, pyridylphenyl, methoxyphenyl, chlorophenyl, aminophenyl, etc., wherein the nitro, pyridyl, methoxy, chloro, and amino groups may replace any suitable hydrogen on the phenyl ring.

The term "substituted" used as a suffix of a first structure, molecule or group, followed by one or more names of chemical groups refers to a second structure, molecule or group, which is a result of replacing one or more hydrogens of the first structure, molecule or group with the one or more named chemical groups. For example, a "phenyl substituted by nitro" refers to nitrophenyl.

The term "optionally substituted" refers to both groups, structures, or molecules that are substituted and those that are not substituted.

Heterocycle includes, for example, monocyclic heterocycles such as: aziridine, oxirane, thiirane, azetidine, oxetane, thietane, pyrrolidine, pyrroline, imidazolidine, pyrazolidine, pyrazoline, dioxolane, sulfolane 2,3-dihydrofuran, 2,5-dihydrofuran tetrahydrofuran, thiophane, piperidine, 1,2,3,6-tetrahydro-pyridine, piperazine, morpholine, thiomorpholine, pyran, thiopyran, 2,3-dihydropyran, tetrahydropyran, 1,4-dihydropyridine, 1,4-dioxane, 1,3-dioxane, dioxane, homopiperidine, 2,3,4,7-tetrahydro-1*H*-azepine homopiperazine, 1,3-dioxepane, 4,7-dihydro-1,3-dioxepin, and hexamethylene oxide.

In addition, heterocycle includes aromatic heterocycles, for example, pyridine, pyrazine, pyrimidine, pyridazine, thiophene, furan, furazan, pyrrole, imidazole, thiazole, oxazole, pyrazole, isothiazole, isoxazole, 1,2,3-triazole, tetrazole, 1,2,3-thiadiazole, 1,2,3-oxadiazole, 1,2,4-triazole, 1,2,4-thiadiazole, 1,2,4-oxadiazole, 1,3,4-triazole, 1,3,4-thiadiazole, and 1,3,4- oxadiazole.

Additionally, heterocycle encompass polycyclic heterocycles, for example, indole, indoline, isoindoline, quinoline, tetrahydroquinoline, isoquinoline,

tetrahydroisoquinoline, 1,4-benzodioxan, coumarin, dihydrocoumarin, benzofuran, 2,3-dihydrobenzofuran, isobenzofuran, chromene, chroman, isochroman, xanthene, phenoxathiin, thianthrene, indolizine, isoindole, indazole, purine, phthalazine, naphthyridine, quinoxaline, quinazoline, cinnoline, pteridine, phenanthridine, perimidine, phenanthroline, phenazine, phenothiazine, phenoxazine, 1,2-benzisoxazole, benzothiophene, benzoxazole, benzthiazole, benzimidazole, benztriazole, thioxanthine, carbazole, carboline, acridine, pyrolizidine, and quinolizidine.

In addition to the polycyclic heterocycles described above, heterocycle includes polycyclic heterocycles wherein the ring fusion between two or more rings includes more than one bond common to both rings and more than two atoms common to both rings. Examples of such bridged heterocycles include quinuclidine, diazabicyclo[2.2.1]heptane and 7-oxabicyclo[2.2.1]heptane.

Heterocyclyl includes, for example, monocyclic heterocyclyls, such as: aziridinyl, oxiranyl, thiiranyl, azetidinyl, oxetanyl, thietanyl, pyrrolidinyl, pyrrolinyl, imidazolidinyl, pyrazolidinyl, pyrazolinyl, dioxolanyl, sulfolanyl, 2,3-dihydrofuranyl, 2,5-dihydrofuranyl, tetrahydrofuranyl, thiophanyl, piperidinyl, 1,2,3,6-tetrahydro-pyridinyl, piperazinyl, morpholinyl, thiomorpholinyl, pyranyl, thiopyranyl, 2,3-dihydropyranyl, tetrahydropyranyl, 1,4-dihydropyridinyl, 1,4-dioxanyl, 1,3-dioxanyl, dioxanyl, homopiperidinyl, 2,3,4,7-tetrahydro-1*H*-azepinyl, homopiperazinyl, 1,3-dioxepanyl, 4,7-dihydro-1,3-dioxepinyl, and hexamethylene oxidyl.

In addition, heterocyclyl includes aromatic heterocyclyls or heteroaryl, for example, pyridinyl, pyrazinyl, pyrimidinyl, pyridazinyl, thienyl, furyl, furazanyl, pyrrolyl, imidazolyl, thiazolyl, oxazolyl, pyrazolyl, isothiazolyl, isoxazolyl, 1,2,3-triazolyl, tetrazolyl, 1,2,3-thiadiazolyl, 1,2,3-oxadiazolyl, 1,2,4-triazolyl, 1,2,4-thiadiazolyl, 1,2,4-oxadiazolyl, 1,3,4-triazolyl, 1,3,4-thiadiazolyl, and 1,3,4 oxadiazolyl.

Additionally, heterocyclyl encompasses polycyclic heterocyclyls (including both aromatic or non-aromatic), for example, indolyl, indolinyl, isoindolinyl, quinolinyl, tetrahydroquinolinyl, isoquinolinyl, tetrahydroisoquinolinyl, 1,4-benzodioxanyl, coumarinyl, dihydrocoumarinyl, benzofuranyl, 2,3-dihydrobenzofuranyl, isobenzofuranyl, chromenyl, chromanyl, isochromanyl, xanthenyl, phenoxathiinyl, thianthrenyl, indolizinyl, isoindolyl, indazolyl, purinyl,

phthalazinyl, naphthyridinyl, quinoxalinyl, quinazolinyl, cinnolinyl, pteridinyl, phenanthridinyl, perimidinyl, phenanthrolinyl, phenazinyl, phenothiazinyl, phenoxazinyl, 1,2-benzisoxazolyl, benzothiophenyl, benzoxazolyl, benzthiazolyl, benzimidazolyl, benztriazolyl, thioxanthinyl, carbazolyl, carbolinyl, acridinyl, pyrolizidinyl, and quinolizidinyl.

In addition to the polycyclic heterocyclyls described above, heterocyclyl includes polycyclic heterocyclyls wherein the ring fusion between two or more rings includes more than one bond common to both rings and more than two atoms common to both rings. Examples of such bridged heterocycles include quinuclidinyl, diazabicyclo[2.2.1]heptyl; and 7-oxabicyclo[2.2.1]heptyl.

The term "alkoxy" used alone or as a suffix or prefix, refers to radicals of the general formula –O-R, wherein -R is selected from a hydrocarbon radical. Exemplary alkoxy includes methoxy, ethoxy, propoxy, isopropoxy, butoxy, t-butoxy, isobutoxy, cyclopropylmethoxy, allyloxy, and propargyloxy.

The term "aryloxy" used alone or as suffix or prefix, refers to radicals of the general formula –O-Ar, wherein -Ar is an aryl.

The term "heteroaryloxy" used alone or as suffix or prefix, refers to radicals of the general formula –O-Ar', wherein -Ar' is a heteroaryl.

The term "amine" or "amino" used alone or as a suffix or prefix, refers to radicals of the general formula –NRR', wherein R and R' are independently selected from hydrogen or a hydrocarbon radical.

"Acyl" used alone, as a prefix or suffix, means –C(=O)-R, wherein -R is an optionally substituted hydrocarbyl, hydrogen, amino or alkoxy. Acyl groups include, for example, acetyl, propionyl, benzoyl, phenyl acetyl, carboethoxy, and dimethylcarbamoyl.

Halogen includes fluorine, chlorine, bromine and iodine.

"Halogenated," used as a prefix of a group, means one or more hydrogens on the group is replaced with one or more halogens.

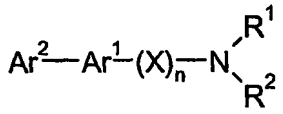
"RT" or "rt" means room temperature.

A first ring group being "fused" with a second ring group means the first ring and the second ring share at least two atoms therebetween.

"Link," "linked," or "linking," unless otherwise specified, means covalently linked or bonded.

Description of Preferred Embodiments

In one aspect, the invention provides a compound of formula I, a pharmaceutically acceptable salt thereof, diastereomers, enantiomers, or mixtures thereof:



I

wherein

Ar^1 is arylene, heteroarylene, substituted arylene or substituted heteroarylene, wherein a ring atom of Ar^1 connected to Ar^2 is seperated from a ring atom of Ar^1 connected to X by at least one atom;

Ar^2 is aryl, heteroaryl, substituted aryl or substituted heteroaryl;

n is 0 or 1;

X is a divalent group that separates groups connected thereto by one or two atoms;

R^1 is a monovalent C_{1-20} group comprising one or more heteroatoms selected from S, O, N and P;

R^2 is hydrogen, C_{1-10} alkyl, C_{1-10}acyl, substituted C_{1-10}acyl, substituted C_{1-10} alkyl, C_{1-10} alkylene, or substituted C_{1-10} alkylene, wherein said alkylene is linked to a ring carbon of Ar^1.

Particularly, the compounds of the present invention are those of formula I, wherein

Ar^1 is an arylene, heteroarylene, substituted arylene or substituted heteroarylene, wherein a ring atom of Ar^1 connected to Ar^2 is seperated from a ring atom of Ar^1 connected to X by at least one atom;

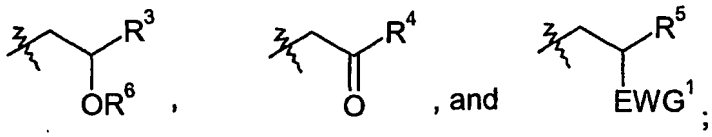
Ar^2 is an aryl, heteroaryl, substituted aryl or substituted heteroaryl;

X is $-CH_2-$, or $-CH_2-CH_2-$;

R^2 is C_{1-6} alkyl, substituted C_{1-6} alkyl, C_{1-3} alkylene, or substituted C_{1-3} alkylene, wherein said alkylene is linked to a ring carbon of Ar^1.

More particularly, the compounds of the present invention are those of formula I, wherein

R^1 is selected from:



wherein R^3 is optionally hydrogen, substituted C_{1-10}alkyl, optionally substituted C_{5-12}aryl, optionally substituted C_{3-10}heteroaryl, optionally substituted aryloxy-C_{1-6}alkyl, optionally substituted heteroaryloxy-C_{1-6}alkyl;

R^4 and R^5 are, independently, hydrogen, optionally substituted C_{1-10}alkyl, optionally substituted C_{5-12}aryl, optionally substituted C_{3-10}heteroaryl, amino group, -NHC(=O)-O-R^7, or -NHC(=O)-R^7, wherein R^7 is C_{1-6}alkyl or aryl;

R^6 is hydrogen, optionally substituted C_{1-6}alkyl, or optionally substituted aryl; and

EWG^1 is an electron withdrawing group.

Even more particularly, the compounds of the present invention are those of formula I, wherein

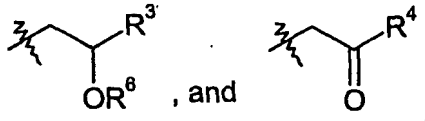
Ar^1 is optionally substituted *para*-phenylene, optionally substituted six-membered *para*-heteroarylene, or optionally substituted monocyclic five-membered *meta*-heteroarylene;

Ar^2 is optionally substituted phenyl, or optionally substituted monocylic five or six-membered heteroaryl;

X is $-CH_2-$, or $-CH_2-CH_2-$;

R^2 is C_{1-3} alkyl, substituted C_{1-3} alkyl, C_{1-3} alkylene, or substituted C_{1-3} alkylene, wherein said alkylene is linked to a ring carbon of Ar^1.

R^1 is selected from:



wherein R^3 is optionally substituted C_{1-6}alkyl, optionally substituted phenyl, optionally substituted phenoxy-methyl;

R^4 is, independently, optionally substituted C_{1-6}alkyl, optionally substituted phenyl, amino, -NHC(=O)-O-R^7, or -NHC(=O)-R^7, wherein R^7 is C_{1-6}alkyl or phenyl; and

R^6 is hydrogen, methyl or ethyl.

Most particularly, the compounds of the present invention are those of formula I, wherein

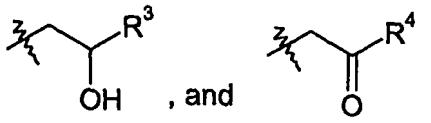
Ar^1 is *para*-phenylene or *para*-pyridylene;

Ar^2 is a phenyl *ortho*-substituted with an electron withdrawing group, or a thienyl *ortho*-substituted with an electron withdrawing group; Even more particularly, Ar^2 is a phenyl *ortho*-substituted with -Cl, -F, -OMe, -OEt, -O-$CH(CH_3)_2$, $-CF_3$, $-NO_2$, or -CN; or thienyl *ortho*-substituted with -Cl, -F, -OMe, -OEt, -O-$CH(CH_3)_2$, $-CF_3$, $-NO_2$, -CN, wherein said *ortho*-substituted Ar^2 is optionally further substituted at its non-*ortho* position;

X is $-CH_2-$;

R^2 is methyl.

R^1 is selected from:

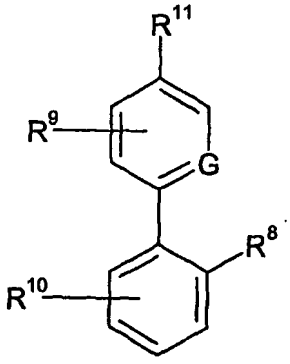


,

wherein R^3 is optionally substituted phenyl, or optionally substituted phenoxymethyl; Even more particularly, R^3 is phenyl, substituted phenoxymethyl or substituted phenyl; and

R^4 is -NHC(=O)-O-R^7, wherein R^7 is C_{1-6}alkyl.

In another aspect, the present invention provides a compound of formula II, or a pharmaceutically acceptable salt thereof:



II

wherein

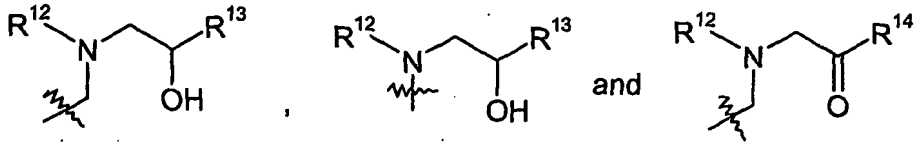
G is N or CH;

R^8 is selected from –H, $-CH_3$, $-CF_3$, $-NO_2$ and –CN;

R^9 is selected from –H and C_{1-3}alkyl;

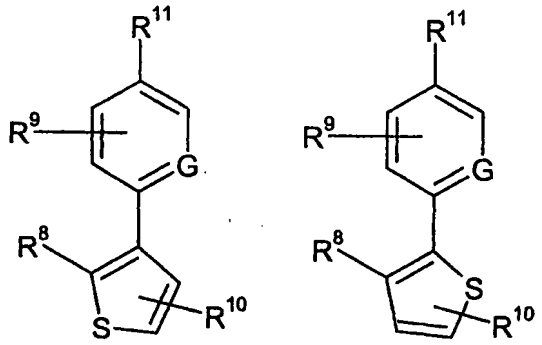
R^{10} is selected from –H and C_{1-3}alkyl; and

R^{11} is selected from



wherein R^{12} is H or methyl, R^{13} is phenyl or substituted phenoxymethyl, R^{14} is –NHC(=O)OR^{15}, wherein R^{15} is C_{1-6}alkyl.

In a further aspect, the present invention provides a compound of formula III or IV, or a pharmaceutically acceptable salt thereof:



III IV

wherein

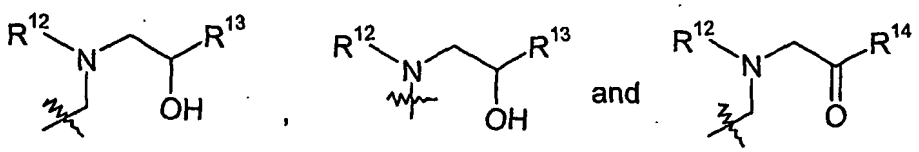
G is N or CH;

R^8 is selected from –H, $-CH_3$, $-CF_3$, $-NO_2$ and –CN;

R^9 is selected from –H and C_{1-3}alkyl;

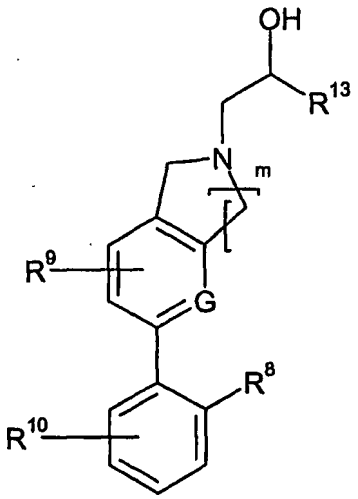
R^{10} is selected from –H and C_{1-3}alkyl; and

R^{11} is selected from



wherein R^{12} is H or methyl, R^{13} is phenyl or substituted phenoxymethyl, R^{14} is –NHC(=O)OR^{15}, wherein R^{15} is C_{1-6}alkyl.

In an even further aspect, the present invention provides a compound of formula V, or a pharmaceutically acceptable salt thereof:



V

wherein

G is N or CH;

m is 1 or 2;

R^8 is selected from –H, $-CH_3$, $-CF_3$, $-NO_2$ and –CN;

R^9 is selected from –H and C_{1-3}alkyl;

R^{10} is selected from –H and C_{1-3}alkyl; and

R^{13} is phenyl or substituted phenoxymethyl.

It will be understood that when compounds of the present invention contain one or more chiral centers, the compounds of the invention may exist in, and be isolated as, enantiomeric or diastereomeric forms, or as a racemic mixture. The present invention includes any possible enantiomers, diastereomers, racemates or mixtures thereof, of a compound of Formula I, II, III, IV or V. The optically active forms of the compound of the invention may be prepared, for example, by chiral chromatographic separation of a racemate, by synthesis from optically active starting materials or by asymmetric synthesis based on the procedures described thereafter.

It will also be appreciated that certain compounds of the present invention may exist as geometrical isomers, for example E and Z isomers of alkenes. The present

invention includes any geometrical isomer of a compound of Formula I, II, III, IV or V. It will further be understood that the present invention encompasses tautomers of the compounds of the formula I, II, III, IV or V.

It will also be understood that certain compounds of the present invention may exist in solvated, for example hydrated, as well as unsolvated forms. It will further be understood that the present invention encompasses all such solvated forms of the compounds of the formula I, II, III, IV or V.

Within the scope of the invention are also salts of the compounds of the formula I, II, III, IV or V. Generally, pharmaceutically acceptable salts of compounds of the present invention may be obtained using standard procedures well known in the art, for example by reacting a sufficiently basic compound, for example an alkyl amine with a suitable acid, for example, HCl or acetic acid, to afford a physiologically acceptable anion. It may also be possible to make a corresponding alkali metal (such as sodium, potassium, or lithium) or an alkaline earth metal (such as a calcium) salt by treating a compound of the present invention having a suitably acidic proton, such as a carboxylic acid or a phenol with one equivalent of an alkali metal or alkaline earth metal hydroxide or alkoxide (such as the ethoxide or methoxide), or a suitably basic organic amine (such as choline or meglumine) in an aqueous medium, followed by conventional purification techniques.

In one embodiment, the compound of formula I, II, III, IV or V above may be converted to a pharmaceutically acceptable salt or solvate thereof, particularly, an acid addition salt such as a hydrochloride, hydrobromide, phosphate, acetate, fumarate, maleate, tartrate, citrate, methanesulphonate or *p*-toluenesulphonate.

We have now found that the compounds of the invention have activity as pharmaceuticals, in particular as modulators or ligands such as agonists, partial agonists, inverse agonist or antagonists of CB_1/CB_2 receptors. More particularly, the compounds of the invention exhibit selective activity as agonist of the CB_1/CB_2 receptors, and are useful in the relief of pain, particularly chronic pain, e.g., chronic inflammatory pain, neuropathic pain, back pain, cancer pain and visceral pain. Compounds of the present invention will also be useful in treating acute pain. Additionally, compounds of the present invention are useful in other disease states in which degeneration or dysfunction of CB_1/CB_2 receptors is present or implicated.

Thus, the invention provides a compound of formula I, II, III, IV or V, or pharmaceutically acceptable salt or solvate thereof, as hereinbefore defined for use in therapy.

In a further aspect, the present invention provides the use of a compound of formula I, II, III, IV or V, or a pharmaceutically acceptable salt or solvate thereof, as hereinbefore defined in the manufacture of a medicament for use in therapy.

In the context of the present specification, the term "therapy" also includes "prophylaxis" unless there are specific indications to the contrary. The term "therapeutic" and "therapeutically" should be contrued accordingly. The term "therapy" within the context of the present invention further encompasses to administer an effective amount of a compound of the present invention, to mitigate either a pre-existing disease state, acute or chronic, or a recurring condition. This definition also encompasses prophylactic therapies for prevention of recurring conditions and continued therapy for chronic disorders.

The compounds of the present invention are useful in therapy, especially for the therapy of various pain conditions including, but not limited to: acute pain, chronic pain, neuropathic pain, acute pain, back pain, cancer pain, and visceral pain.

In use for therapy in a warm-blooded animal such as a human, the compound of the invention may be administered in the form of a conventional pharmaceutical composition by any route including orally, intramuscularly, subcutaneously, topically, intranasally, intraperitoneally, intrathoracially, intravenously, epidurally, intrathecally, intracerebroventricularly and by injection into the joints.

In one embodiment of the invention, the route of administration may be orally, intravenously or intramuscularly.

The dosage will depend on the route of administration, the severity of the disease, age and weight of the patient and other factors normally considered by the attending physician, when determining the individual regimen and dosage level at the most appropriate for a particular patient.

For preparing pharmaceutical compositions from the compounds of this invention, inert, pharmaceutically acceptable carriers can be either solid and liquid. Solid form preparations include powders, tablets, dispersible granules, capsules, cachets, and suppositories.

A solid carrier can be one or more substances, which may also act as diluents, flavoring agents, solubilizers, lubricants, suspending agents, binders, or table disintegrating agents; it can also be an encapsulating material.

In powders, the carrier is a finely divided solid, which is in a mixture with the finely divided compound of the invention, or the active component. In tablets, the active component is mixed with the carrier having the necessary binding properties in suitable proportions and compacted in the shape and size desired.

For preparing suppository compositions, a low-melting wax such as a mixture of fatty acid glycerides and cocoa butter is first melted and the active ingredient is dispersed therein by, for example, stirring. The molten homogeneous mixture in then poured into convenient sized moulds and allowed to cool and solidify.

Suitable carriers are magnesium carbonate, magnesium stearate, talc, lactose, sugar, pectin, dextrin, starch, tragacanth, methyl cellulose, sodium carboxymethyl cellulose, a low-melting wax, cocoa butter, and the like.

The term composition is also intended to include the formulation of the active component with encapsulating material as a carrier providing a capsule in which the active component (with or without other carriers) is surrounded by a carrier which is thus in association with it. Similarly, cachets are included.

Tablets, powders, cachets, and capsules can be used as solid dosage forms suitable for oral administration.

Liquid form compositions include solutions, suspensions, and emulsions. For example, sterile water or water propylene glycol solutions of the active compounds may be liquid preparations suitable for parenteral administration. Liquid compositions can also be formulated in solution in aqueous polyethylene glycol solution.

Aqueous solutions for oral administration can be prepared by dissolving the active component in water and adding suitable colorants, flavoring agents, stabilizers, and thickening agents as desired. Aqueous suspensions for oral use can be made by dispersing the finely divided active component in water together with a viscous material such as natural synthetic gums, resins, methyl cellulose, sodium carboxymethyl cellulose, and other suspending agents known to the pharmaceutical formulation art.

Depending on the mode of administration, the pharmaceutical composition will preferably include from 0.05% to 99%w (per cent by weight), more preferably from 0.10 to 50%w, of the compound of the invention, all percentages by weight being based on total composition.

A therapeutically effective amount for the practice of the present invention may be determined, by the use of known criteria including the age, weight and response of the individual patient, and interpreted within the context of the disease which is being treated or which is being prevented, by one of ordinary skills in the art.

Within the scope of the invention is the use of any compound of formula I, II, III, IV or V as defined above for the manufacture of a medicament.

Also within the scope of the invention is the use of any compound of formula I, II, III, IV or V for the manufacture of a medicament for the therapy of pain.

Additionally provided is the use of any compound according to Formula I, II, III, IV or V for the manufacture of a medicament for the therapy of various pain conditions including, but not limited to: acute pain, chronic pain, neuropathic pain, acute pain, back pain, cancer pain, and visceral pain.

A further aspect of the invention is a method for therapy of a subject suffering from any of the conditions discussed above, whereby an effective amount of a compound according to the formula I, II, III, IV or V above, is administered to a patient in need of such therapy.

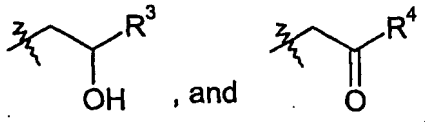
Additionally, there is provided a pharmaceutical composition comprising a compound of Formula I, II, III, IV or V, or a pharmaceutically acceptable salt thereof, in association with a pharmaceutically acceptable carrier.

Particularly, there is provided a pharmaceutical composition comprising a compound of Formula I, II, III, IV or V, or a pharmaceutically acceptable salt thereof, in association with a pharmaceutically acceptable carrier for therapy, more particularly for therapy of pain.

Further, there is provided a pharmaceutical composition comprising a compound of Formula I, II, III, IV or V, or a pharmaceutically acceptable salt thereof, in association with a pharmaceutically acceptable carrier use in any of the conditions discussed above.

In a further aspect, the present invention provides a method of preparing a compound of the present invention using one or more of the general procedures

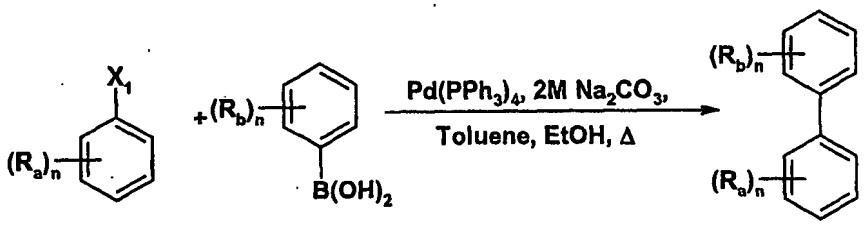
below, wherein R_a and R_b are independently selected from –H, optionally substituted C_{1-6}alkyl, optionally substituted aryl, optionally substituted heteroaryl, $-CF_3$, $-NO_2$, and –CN; n is 1 or 2; R_c, R_d, R_e and R_f are independently selected from –H, C_{1-3}alkyl,



wherein R^3 is optionally substituted phenyl, or optionally substituted phenoxymethyl;

R^4 is -NHC(=O)-O-R^7, wherein R^7 is C_{1-6}alkyl; R_{c1} is –H or C_{1-3}alkyl; and R_g is optionally subsitituted phenyl or optionally subsituted phenoxymethyl.

General Procedure 1:

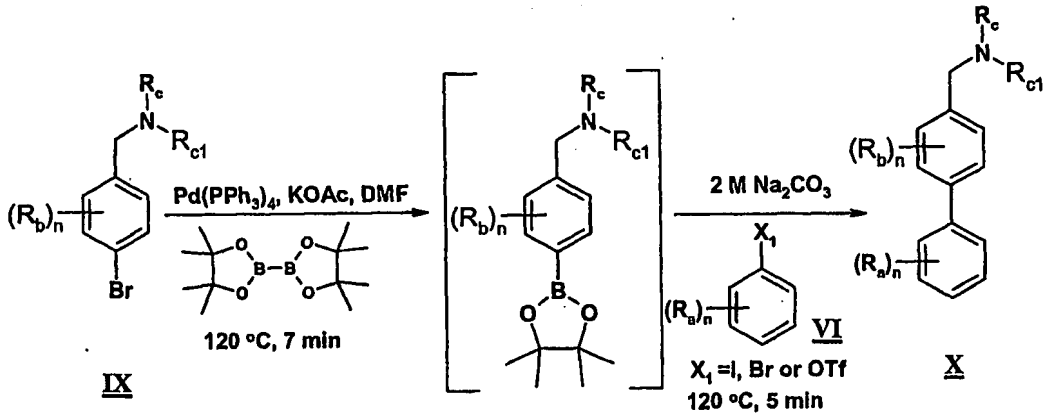


VI VII VIII

X_1 =I or Br

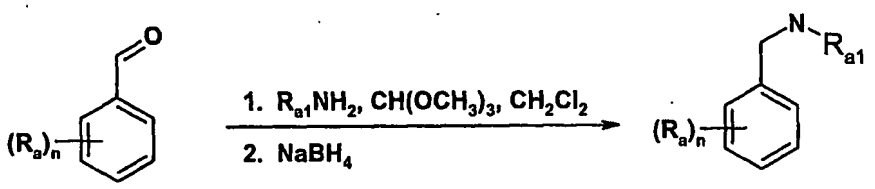
A solution of the aryl boronic acid (VII, 1.5 equiv.) in ethanol (3 mL/mmol boronic acid) was added to a mixture of the aryl halide (VI, 1 equiv.), $Pd(PPh_3)_4$ (0.05 equiv.), toluene (9 mL/mmol aryl halide), and 2 M Na_2CO_3 (6.7 equiv.). The resulting mixture was heated at reflux until the aryl halide was consumed (typically 16 h). The reaction was then concentrated *in vacuo*, and the residue was diluted with water. The aqueous phase was extracted with EtOAc (3x). The combined organic phases were then washed with brine, dried over $MgSO_4$, filtered through Celite, and concentrated *in vacuo*. The residue was dissolved in methanol and allowed to stand overnight. The orange solid which precipitated was filtered, and the supernatant was concentrated *in vacuo* to provide the title compound. The product (VIII) was used for subsequent steps, or purified by silica gel column chromatography when necessary.

General Procedure 2:



Solutions of the aryl bromide (IX, 1 equiv.) in DMF (3 mL/mmol aryl bromide) and bis(pinacolato)diboron (1.1 equiv.) in DMF (2.7 mL/mmol diboron compound) were added successively to a mixture of $Pd(PPh_3)_4$ (0.03 equiv.) and KOAc (3 equiv.) contained in a microwave process vial. The vial was capped and heated to 120 °C for 7 min using microwave irradiation. The resulting mixture was cooled, and 2 M Na_2CO_3 (4.9 equiv.) and a solution of the second aryl halide or aryl triflate (VI, 1-2 equiv.) in DMF (0.3-0.9 mL/mmol aryl halide/triflate, depending on solubility) were added to the vial through the septum cap. The reaction was heated to 120 °C for an additional 5 minutes using microwave irradiation. The resulting mixture was diluted with water (6 mL/mmol of initial aryl halide used) and CH_2Cl_2 (24 mL/mmol of initial aryl halide used), loaded onto an Extube® Chem Elut column (Varian), and eluted with two column volumes of CH_2Cl_2. The eluant was concentrated, and the residue was dissolved in CH_2Cl_2 (12 mL/mmol of initial aryl halide used). MP-TsOH resin was added to the solution, and the mixture was stirred for 2 hours. The resin was removed by filtration and washed with additional CH_2Cl_2 and MeOH. The filtrate and washings were discarded, and the compound (X) was then released from the resin using 2M NH_3 in MeOH. The release solution was concentrated to provide the compound (X).

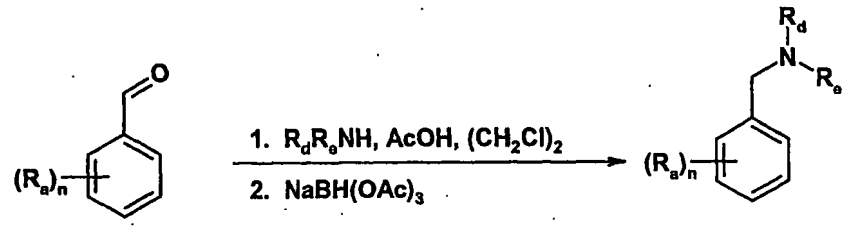
General Procedure 3:



XI XII

A solution of $R_{a1}NH_2$ in MeOH (2 M, 5 equiv.) was added to a mixture of the aldehyde (XI, 1 equiv.) and $CH(OCH_3)_3$ (10 equiv) in CH_2Cl_2 (7.5 mL/mmol aldehyde). The resulting mixture was stirred overnight at room temperature, and then $NaBH_4$ (2.5 equiv.) was added. When the starting aldehyde/intermediate imine had been completely consumed, the reaction was concentrated *in vacuo*. The residue was taken into EtOAc (10 mL/mmol aldehyde used) and the product was extracted into 1 N HCl (3 x 7.5 mL/mmol aldehyde used). The EtOAc layer was discarded, the combined aqueous layers were basicified with 6 N NaOH, and the product was back extracted with EtOAc (3 x 10 mL/mmol aldehyde used). The combined organic phases were then dried over Na_2SO_4, filtered, and concentrated *in vacuo* to provide the compound (XII). The compound (XII) was used for subsequent steps, or purified by silica gel column chromatography when necessary.

General Procedure 4:

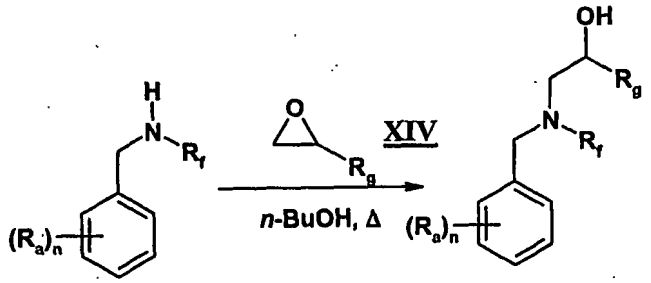


XI XIII

A solution of the amine (R_dR_eNH, 1 equiv.) and aldehyde (XI, 1-2 equiv.) in AcOH/dichloroethane (5% v/v, 10 mL/mmol amine) was stirred at room temperature overnight. $NaBH(OAc)_3$ (2 equiv.) was then added. When the starting aldehyde/intermediate imine/iminium ion had been completely consumed, saturated Na_2CO_3 (6 mL/mmol amine) was added. The layers were separated, and the aqueous

layer was extracted with additional EtOAc (3 x 12 mL/mmol amine). The combined organic phases were then dried over Na_2SO_4, filtered, and concentrated *in vacuo* to provide the compound (XIII). The compound (XIII) was used for subsequent steps, or purified by silica gel column chromatography or reverse phase HPLC when necessary.

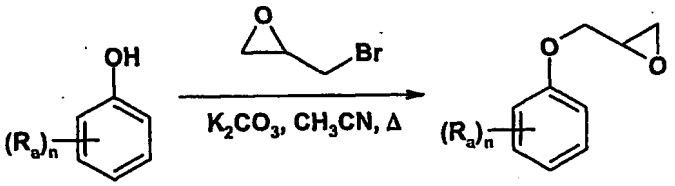
General Procedure 5:



XII XV

A solution of the amine (XII, 1 equiv.) and epoxide (XIV, 1 equiv.) in *n*-BuOH (6 mL/mmol amine) was heated at the temperature specified until the starting materials were consumed. The reaction was concentrated *in vacuo*, and the residue was purified by reverse phase HPLC to provide the compound (XV).

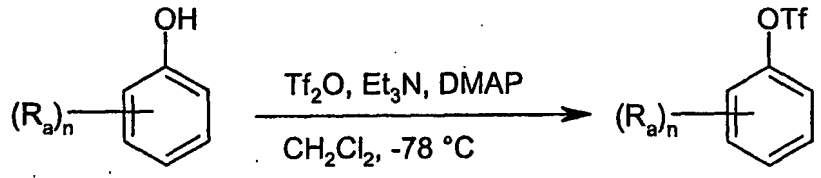
General Procedure 6:



XVI XVII

A suspension of the phenol (XVI, 1 equiv.), epibromohydrin (5 equiv.), and K_2CO_3 (5 equiv.) in dry CH_3CN (8 mL/mmol phenol) was heated at 70 °C until the starting phenol was completely consumed (typically 16 h). The reaction mixture was filtered to remove solids which were then washed with additional CH_3CN. The filtrate was concentrated to provide the compound (XVII).

General Procedure 7:



XVI **XVIII**

Triethylamine (2.2 equiv.), followed by triflic anhydride (1.1 equiv.), was added dropwise to a solution of the phenol (XVI, 1 equiv.) and DMAP (0.1 equiv.) in dry CH_2Cl_2 (10 mL/mmol phenol) maintained at –78°C. The reaction was allowed to slowly warm to room temperature and stirred until the starting phenol was completely consumed (typically 16 h). Once the reaction was complete, water was added (10 mL/mmol phenol), the layers were separated, and the aqueous phase was extracted with CH_2Cl_2 (2 x 10 mL/mmol phenol). The combined organic phases were then dried over Na_2SO_4, filtered, and concentrated *in vacuo*. Silica gel column chromatography on the organic phase residue provided the compound (XVIII).

The compounds of the invention were found to be active towards CB_1/CB_2 receptors in warm-blooded animal, e.g., human. Particularly the compounds of the invention have been found to be effective CB_1/CB_2 receptor agonists. *In vitro* assays, *infra*, demonstrated these surprising activities. In these *in vitro* assays, a compound is tested for their activity toward CB_1/CB_2 receptors and the dissociation constant (Ki) is obtained to determine the selective activity for a particular compound towards CB_1/CB_2 receptors by measuring IC_{50} of the compound. In the current context, IC_{50} generally refers to the concentration of the compound at which 50% displacement of a standard radioactive CB_1/CB_2 receptor ligand has been observed. Generally, a lower Ki for a particular compound towards CB_1/CB_2 receptors means that the particular compound is a stronger ligand towards the CB_1/CB_2 receptors. As a result, compounds with relatively low Ki towards CB_1/CB_2 receptors are relatively strong CB_1/CB_2 receptor ligands or strong CB_1/CB_2 receptor agonists.

Biological Evaluation

hCB_1 and hCB_2 receptor binding

Human CB_1 receptor from Receptor Biology (hCB1) or human CB_2 receptor from BioSignal (hCB2) membranes are thawed at 37 °C, passed 3 times through a 25-gauge blunt-end needle, diluted in the cannabinoid binding buffer (50 mM Tris, 2.5 mM EDTA, 5 mM $MgCl_2$, and 0.5 mg/mL BSA fatty acid free, pH 7.4) and aliquots containing the appropriate amount of protein are distributed in 96-well plates. The IC_{50} of the compounds of the invention at hCB_1 and hCB_2 are evaluated from 10-point dose-response curves done with ^{3}H-CP55,940 at 20000 to 25000 dpm per well (0.17-0.21 nM) in a final volume of 300 µl. The total and non-specific binding are determined in the absence and presence of 0.2 µM of HU210 respectively. The plates are vortexed and incubated for 60 minutes at room temperature, filtered through Unifilters GF/B (presoaked in 0.1% polyethyleneimine) with the Tomtec or Packard harvester using 3 mL of wash buffer (50 mM Tris, 5 mM $MgCl_2$, 0.5 mg BSA pH 7.0). The filters are dried for 1 hour at 55 °C. The radioactivity (cpm) is counted in a TopCount (Packard) after adding 65 µl/well of MS-20 scintillation liquid.

Based on the above assays, the dissociation constant (Ki) for a particular compound of the invention towards a particular receptor is determined using the following equation:

$Ki = IC_{50}/(1+[rad]/Kd)$,

Wherein IC_{50} is the concentration of the compound of the invention at which 50% displacement has been observed;

[rad] is a standard or reference radioactive ligand concentration at that moment; and

Kd is the dissociation constant of the radioactive ligand towards the particular receptor.

Biological data for certain compounds of the invention are listed in Table 1 below.

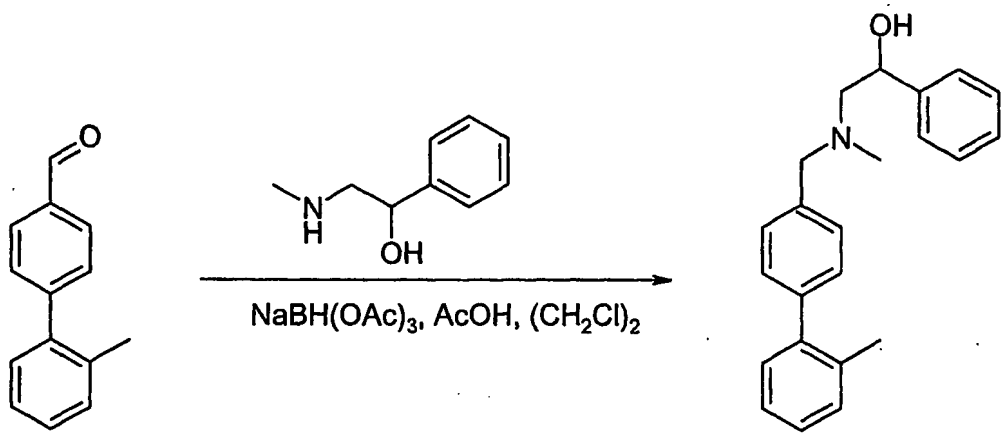
Table 1

Compound No.	CB_2 (Ki, nM)	CB_1 (Ki, nM)
1-132	15-2800	50-5000

EXAMPLES

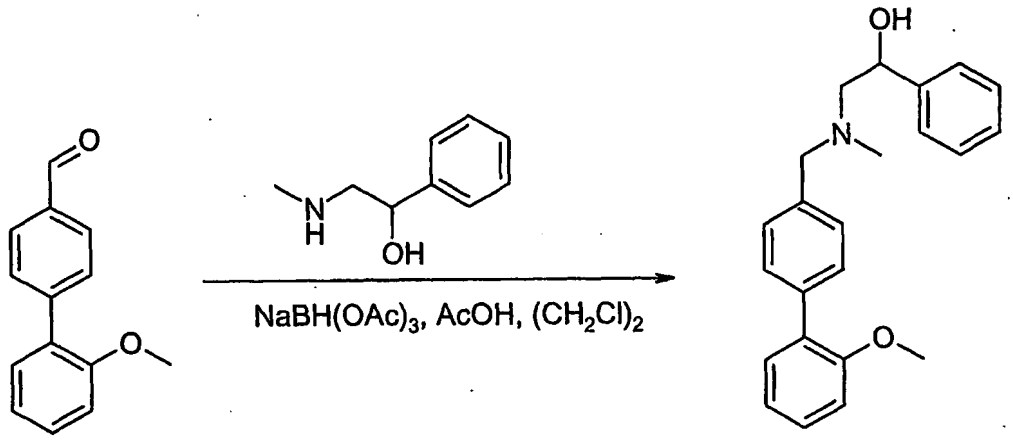
The invention will further be described in more detail by the following Examples which describe methods whereby compounds of the present invention may be prepared, purified, analyzed and biologically tested, and which are not to be construed as limiting the invention.

Example 1: α-[[Methyl[(2'-methyl[1,1'-biphenyl]-4-yl)methyl]amino]methyl]-benzenemethanol



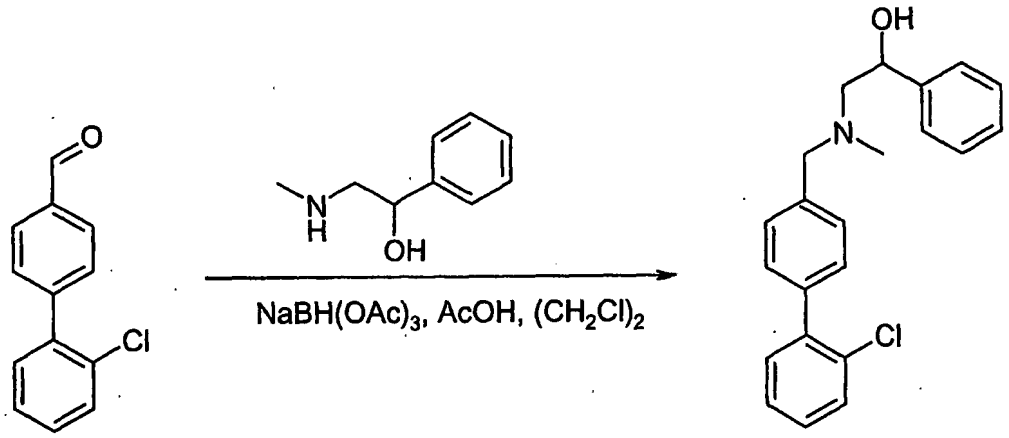
Following General Procedure 4, 2'-methyl-[1,1'-biphenyl]-4-carboxaldehyde (0.250 g, 1.28 mmol), α-[(methylamino)methyl]benzenemethanol (0.363 g, 2.40 mmol), and $NaBH(OAc)_3$ (0.506 g, 2.40 mmol) were combined. When the starting imine intermediate had been completely consumed, 1 N NaOH (10 mL/mmol amine) was added. The layers were then filtered through a Hydromatrix®column and the product was eluted with CH_2Cl_2. The organic phase was concentrated *in vacuo* and purified by reverse phase HPLC (gradient 20-100% CH_3CN in H_2O) to provide the title compound (0.052 g, 11%) as its HCO_2H salt. Due to quaternization of the stereogenic nitrogen atom, a mixture of 2 diastereomeric salts was obtained. ^{1}H-NMR ($CDCl_3$): δ 7.39-7.23 (br m, 13H), 4.83 (dd, *J*=3.8 Hz, *J*=10.2 Hz, 1H), 3.94-3.85 (overlapping br s at 3.94 and d at 3.87, *J*=13.2 Hz, 2H), 3.68 (d, *J*=12.8 Hz, 1H), 2.72 (dd, *J*=10.0 Hz, *J*=12.4 Hz, 1H), 2.63 (dd, *J*=3.6 Hz, *J*=12.0 Hz, 1H), 2.44 (s, 3H), 2.28 (s, 3H). MS (ESI) $(M+H)^+ = 332$. Anal. Calcd for $C_{23}H_{25}NO + 0.30$ CH_2O_2: C, 81.06; H, 7.47; N, 4.06. Found: C, 81.40; H, 7.76; N, 4.18.

Example 2: α-[[[(2'-Methoxy[1,1'-biphenyl]-4-yl)methyl]methylamino]methyl]-benzenemethanol



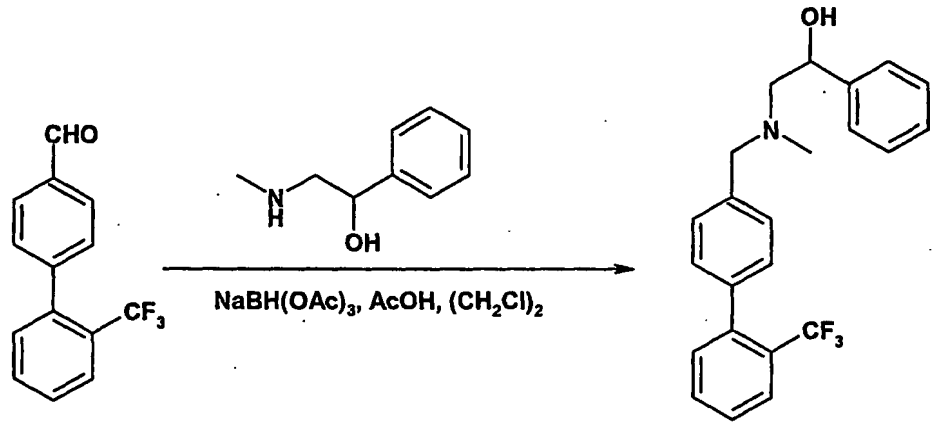
Following General Procedure 4, 2'-methoxy-[1,1'-biphenyl]-4-carboxaldehyde (0.250 g, 1.18 mmol), α-[(methylamino)methyl]benzenemethanol (0.363 g, 2.40 mmol), and $NaBH(OAc)_3$ (0.506 g, 2.40 mmol) were combined. When the starting imine intermediate had been completely consumed, 1 N NaOH (10 mL/mmol amine) was added. The layers were then filtered through a Hydromatrix® column and the product was eluted with CH_2Cl_2. The organic phase was concentrated *in vacuo* and purified by reverse phase HPLC (gradient 20-100% CH_3CN in H_2O) to provide the title compound (0.048 g, 10%) as its HCO_2H salt. Due to quaternization of the stereogenic nitrogen atom, a mixture of 2 diastereomeric salts was obtained. ^{1}H-NMR ($CDCl_3$): δ 7.54 (d, *J*=8.4 Hz, 2H), 7.40-7.25 (br m, 9H), 7.05-6.98 (m, 2H), 4.88 (dd, *J*=2.6 Hz, *J*=10.2 Hz, 1H), 4.55 (br s, 1H), 3.91 (d, *J*=13.6 Hz, 1H), 3.81-3.74 (overlapping s at 3.81 and d at 3.75, *J*=13.2 Hz, 4H), 2.79 (dd, *J*=10.0 Hz, *J*=13.2 Hz, 1H), 2.68 (dd, *J*=3.2 Hz, *J*=12.8 Hz, 1H), 2.48 (s, 3H). MS (ESI) $(M+H)^+$ = 348. Anal. Calcd for $C_{23}H_{25}NO_2$ + 0.40 CH_2O_2: C, 76.82; H, 7.11; N, 3.83. Found: C, 76.98; H, 7.17; N, 3.77.

Example 3: α-[[[(2'-Chloro[1,1'-biphenyl]-4-yl)methyl]methylamino]methyl]-benzenemethanol



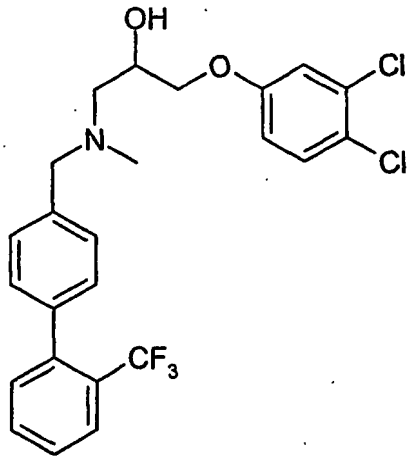
Following General Procedure 4, 2'-chloro-[1,1'-biphenyl]-4-carboxaldehyde (0.250 g, 1.16 mmol), α-[(methylamino)methyl]benzenemethanol (0.363 g, 2.40 mmol), and $NaBH(OAc)_3$ (0.506 g, 2.40 mmol) were combined. When the starting imine intermediate had been completely consumed, 1 N NaOH (10 mL/mmol amine) was added. The layers were then filtered through a Hydromatix® column and the product was eluted with CH_2Cl_2. The organic phase was concentrated *in vacuo* and purified by reverse phase HPLC (gradient 20-100% CH_3CN in H_2O) to provide the title compound (0.050 g, 11%) as its HCO_2H salt. Due to quaternization of the stereogenic nitrogen atom, a mixture of 2 diastereomeric salts was obtained. ^{1}H-NMR ($CDCl_3$): δ 7.49-7.26 (br m, 13H), 4.85 (dd, *J*=3.2 Hz, *J*=10.8 Hz, 1H), 4.18 (br s, 1H), 3.89 (d, *J*=12.8 Hz, 1H), 3.72 (d, *J*=13.2 Hz, 1H), 2.75 (dd, *J*=10.4 Hz, *J*=12.8 Hz, 1H), 2.65 (dd, *J*=3.2 Hz, *J*=12.8 Hz, 1H), 2.46 (s, 3H). MS (ESI) $(M+H)^+$ = 352. Anal. Calcd for $C_{22}H_{22}NOCl + 0.30\ CH_2O_2$: C, 73.25; H, 6.23; N, 3.83. Found: C, 73.44; H, 6.31; N, 3.86.

Example 4: α-[[Methyl-[[2'-(trifluoromethyl)-[1,1'-biphenyl]-4-yl]methyl]amino]methyl]-benzenemethanol

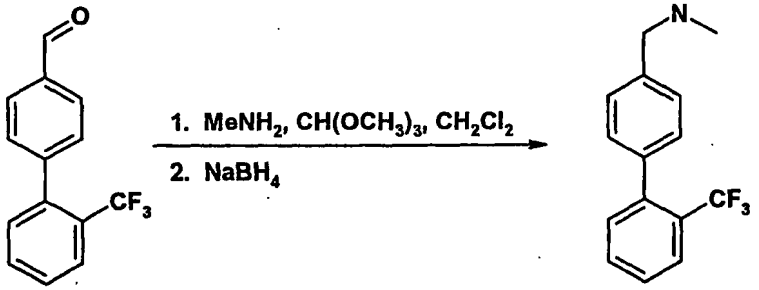


Following General Procedure 4, 2'-(trifluoromethyl)- [1,1'-biphenyl]-4-carboxaldehyde (0.500 g, 2.00 mmol), α-[(methylamino)methyl]benzenemethanol (0.604 g, 4.00 mmol), and $NaBH(OAc)_3$ (0.844 g, 4.00 mmol) were combined. The crude product was purified by flash chromatography (3:7 Hexanes:EtOAc) to provide the title compound. HCl in Et_2O (2 mL of 1M, 2.00 mmol) was added to the compound and the resulting solid was filtered and washed with additional Et_2O to provide the HCl salt (0.558 g, 66%). Due to quaternization of the stereogenic nitrogen atom, a mixture of 2 diastereomeric salts was obtained. ^{1}H-NMR (CD_3OD): δ 7.81 (d, *J*=7.6 Hz, 1H), 7.71-7.56 (m, 4H), 7.52-7.32 (m, 8H), 5.15-5.09 (m, 1H), 4.77 (br d, *J*=14.0 Hz, 0.5H), 4.50 (AB_q, 1H), 4.33 (br d, *J*=12.0 Hz, 0.5H), 3.46-3.15 (m, 2H), 3.08 (s, 1.5H), 2.92 (s, 1.5H). MS (ESI) $(M+H)^+ = 386$. Anal. Calcd for $C_{23}H_{22}F_3NO$+1.1 HCl: C, 64.92; H, 5.47; N, 3.29. Found: C, 65.16; H, 5.63; N, 3.37.

Example 5: 1-(3,4-Dichlorophenoxy)-3-[methyl[[2'-(trifluoromethyl)[1,1'-biphenyl]-4-yl]methyl]amino]- 2-propanol

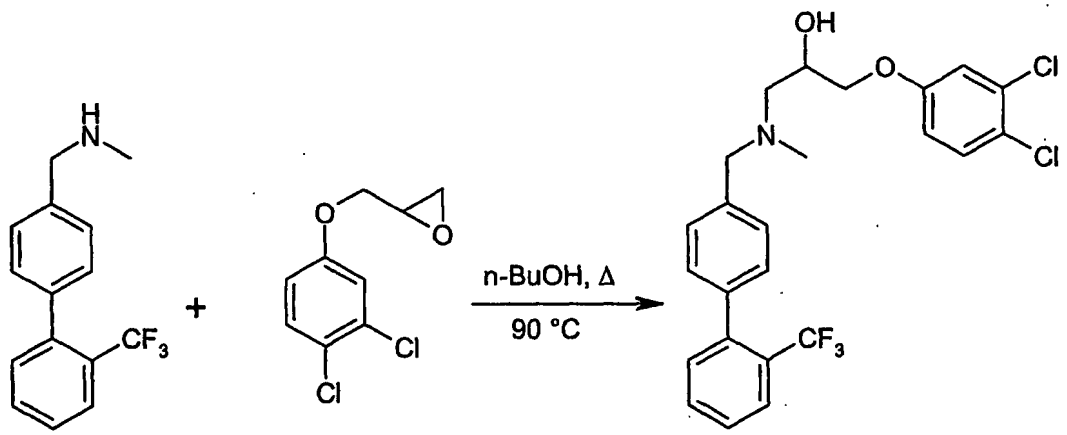


Compound 5A: *N*-Methyl-2'-(trifluoromethyl)- [1,1'-biphenyl]-4-methanamine



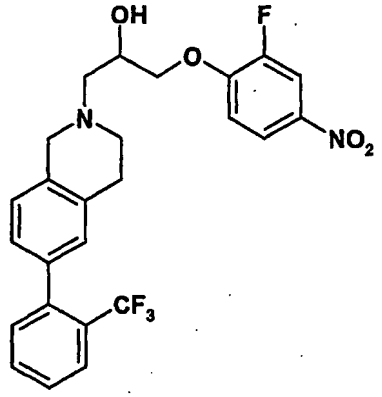
Following General Procedure 3, 2'-(trifluoromethyl)- [1,1'-biphenyl]-4-carboxaldehyde (0.400 g, 1.60 mmol) was converted to the title compound (0.297 g, 70%). The crude material was of sufficient purity (>90%) to be used in subsequent steps. ^{1}H-NMR ($CDCl_3$) δ 7.75 (d, *J*=7.6 Hz, 1H), 7.56 (t, *J*=7.2 Hz, 1H), 7.46 (d, *J*=7.6 Hz, 1H), 7.42-7.28 (m, 5H), 3.82 (s, 2H), 2.51 (s, 3H), 2.13 (br s, 1H). MS (ESI) $(M+H)^+ = 266$.

Compound 5b: 1-(3,4-Dichlorophenoxy)-3-[methyl[[2'-(trifluoromethyl)[1,1'-biphenyl]-4-yl]methyl]amino]- 2-propanol

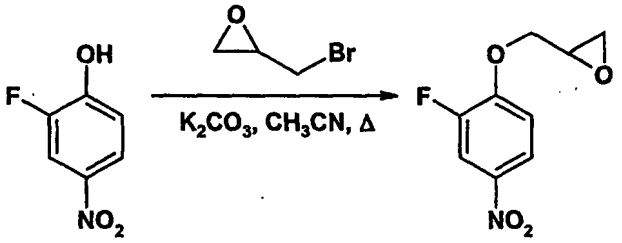


Following General Procedure 5, *N*-methyl-2'-(trifluoromethyl)-[1,1'-biphenyl]-4-methanamine (0.133 g, 0.40 mmol) and 2-[(3,4-dichlorophenoxy)methyl]oxirane (0.088 g, 0.40 mmol) were combined and heated at 50°C for 24 h. The crude product was purified by reverse phase HPLC (gradient 30-70% CH_3CN in H_2O) to provide the title compound (0.026 g, 11%) as its TFA salt. This material was lyophilized from H_2O/ CH_3CN to produce a white solid. ^{1}H-NMR ($CDCl_3$): δ 7.77 (d, *J*=7.6 Hz, 1H), 7.60 (t, *J*=7.4 Hz, 1H), 7.53-7.51 (m, 3H), 7.43 (d, *J*=8.0 Hz, 2H), 7.34-7.31 (overlapping s at 7.33 and d at 7.32, *J*=8.8 Hz, 2H), 6.97 (d, *J*=2.8 Hz, 1H), 6.73 (dd, *J*=2.8 Hz, *J*=8.8 Hz, 1H), 4.50 (br s, 1H), 4.36 (br s, 2H), 4.07 (br s, 1H), 3.89 (t, *J*=8.2 Hz, 1H), 3.51-3.03 (br s at 3.36 and br s at 3.16, 2H), 2.94 (br s, 3H). MS (ESI) $(M+H)^+ = 484$. Anal. Calcd for $C_{24}H_{22}Cl_2F_3NO_2 + 0.3\ H_2O + 0.9$ TFA: C, 52.31; H, 4.00; N, 2.36. Found: C, 52.32; H, 3.93; N, 2.24.

Example 6: α-[(2-Fluoro-4-nitrophenoxy)methyl]-3,4-dihydro-6-[2-(trifluoromethyl)phenyl]-2(1*H*)-isoquinolineethanol

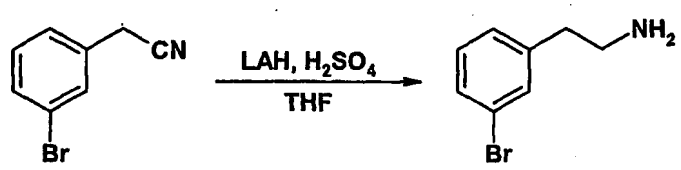


Compound 6a: 2-[(2-Fluoro-4-nitrophenoxy)methyl]oxirane



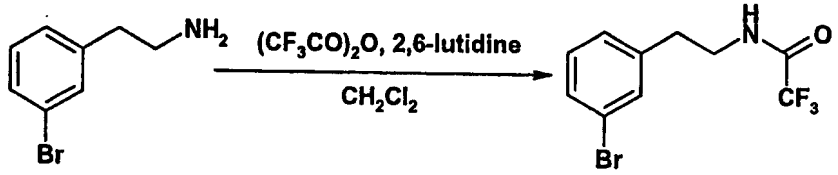
Following General Procedure 6, 2-fluoro-4-nitrophenol (0.471 g, 3.00 mmol) was converted to the title compound (0.635 g, 99%). The crude compound was used for subsequent steps. ^{1}H-NMR ($CDCl_3$): δ 8.06 (ddd, *J*=1.2 Hz, *J*=2.4 Hz, *J*=8.8 Hz, 1H), 8.00 (dd, *J*=2.4 Hz, *J*=10.4 Hz, 1H), 7.10 (dd, *J*=8.0 Hz, *J*=9.2 Hz, 1H), 4.48 (dd, *J*=2.4 Hz, *J*=11.2 Hz, 1H), 4.11 (dd, *J*=6.0 Hz, *J*=11.6 Hz, 1H), 3.45-3.39 (m, 1H), 2.97 (dd, *J*=4.0 Hz, *J*=4.8 Hz, 1H), 2.81 (dd, *J*=2.8 Hz, *J*=4.8 Hz, 1H).

Compound 6b: 3-Bromobenzeneethanamine



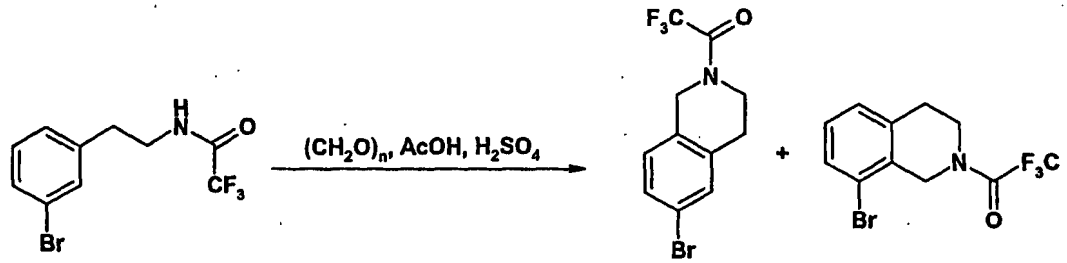
A suspension of $LiAlH_4$ (1.24 g, 32.7 mmol) in dry THF (50 mL) was cooled to 0 °C. Concentrated H_2SO_4 (1.6 g, 16.3 mmol) was added dropwise, and the resulting mixture was stirred at 0 °C for 30 min. A solution of 3-bromo-benzeneacetonitrile (4.01 g, 20.4 mmol) in THF (5 mL) was added dropwise, and the reaction was allowed to warm to room temperature when the addition was complete. The reaction was stirred at room temperature for 1h, and then cooled back to 0 °C and quenched by the addition of a 1:1 THF:H_2O mixture (5 mL). Et_2O was added (20 mL), followed by a 3.6 M solution of NaOH (10 mL). The mixture was filtered through Celite, and the solids were washed well with additional Et_2O. The organic phase was dried over Na_2SO_4, filtered, and concentrated *in vacuo* to provide the title compound (3.91 g, 96%). The crude compound was used in subsequent steps. ^{1}H-NMR ($CDCl_3$): δ 7.38-7.30 (overlapping s at 7.35 and d, *J*=7.2 Hz for d, 2H), 7.20-7.10 (m, 2H), 2.96 (t, *J*=6.8 Hz, 2H), 2.72 (t, *J*=6.4 Hz, 2H), 1.35 (br s, 2H). MS (ESI) $(M+H)^+ = 200/202$.

Compound 6c: ***N*-[2-(3-Bromophenyl)ethyl]-2,2,2-trifluoroacetamide**



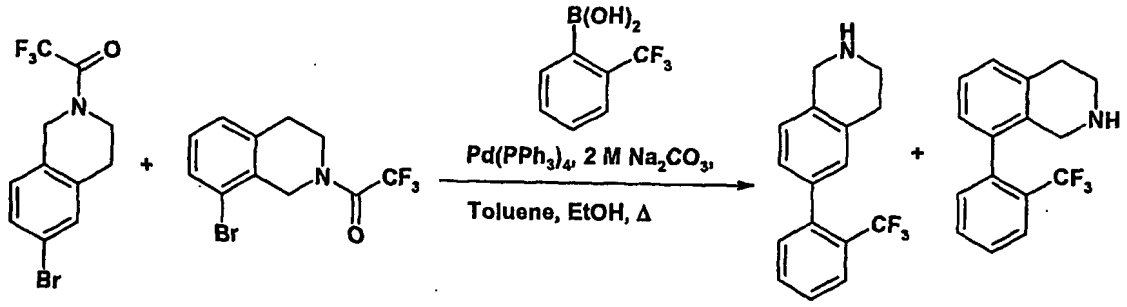
A mixture of 3-bromobenzeneethanamine (2.00 g, 10.0 mmol) and 2,6-lutidine (1.2 mL, 10.3 mmol) in dry CH_2Cl_2 (40 mL) was cooled to 0 °C. Trifluoroacetic anhydride (1.4 mL, 9.9 mmol) was added dropwise, and the reaction was then warmed to room temperature and allowed to stir for 16 h. Water (40 mL) was added to the reaction, the phases were separated, and the aqueous layer was extracted with CH_2Cl_2 (2 x 40 mL). The combined organic phases were washed successively with 1 M HCl (40 mL) and saturated $NaHCO_3$ (40 mL), and then dried over Na_2SO_4, filtered, and concentrated *in vacuo* to provide the title compound (2.93 g, 100%). The crude compound was used in subsequent steps. ^{1}H-NMR ($CDCl_3$): δ 7.40 (d, *J*=8.0 Hz, 1H), 7.36 (s, 1H), 7.21 (t, *J*=7.6 Hz, 1H), 7.12 (d, *J*=7.6 Hz, 1H), 6.33 (br s, 1H), 3.59 (q, *J*=6.8 Hz, 2H), 2.87 (t, *J*=7.2 Hz, 2H). MS (ESI) $(M+H)^+ = 296/298$.

Compound 6d: 6-Bromo-1,2,3,4-tetrahydro-2-(trifluoroacetyl)isoquinoline and 8-bromo-1,2,3,4-tetrahydro-2-(trifluoroacetyl)isoquinoline



A mixture of glacial acetic acid (22.5 mL) and concentrated sulfuric acid (15 mL) was added to a mixture of *N*-[2-(3-bromophenyl)ethyl]-2,2,2-trifluoroacetamide (4.06 g, 13.7 mmol) and paraformaldehyde (0.659 g, 22.0 mmol equiv. of formaldehyde). The reaction was stirred at room temperature for 16 h, and then poured into 300 mL of cold water. The aqueous solution was extracted with EtOAc (3 x 100 mL). The combined organic phases were washed with saturated $NaHCO_3$ (75 mL) and water (2 x 150 mL). The organic phase was then dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The residue was purified by column chromatography (4:1 Hexanes:EtOAc) to provide a mixture of the title compounds (3.31 g, 78%). Due to hindered rotation about the amide bond, rotamers were observed in the ^{1}H-NMR spectrum. ^{1}H-NMR ($CDCl_3$): δ 7.46 (dd, *J*=2.0 Hz, *J*=6.8 Hz, 0.33H), 7.38-7.31 (m, 1.33H), 7.15-7.09 (m, 0.67H), 7.05-6.98 (m, 0.67H), 4.75, 4.73, 4.69 (3 x s, 2H), 3.90-3.80 (m, 2H), 3.00-2.90 (m, 2H). MS (ESI) $(M+H)^+$ = 308/310.

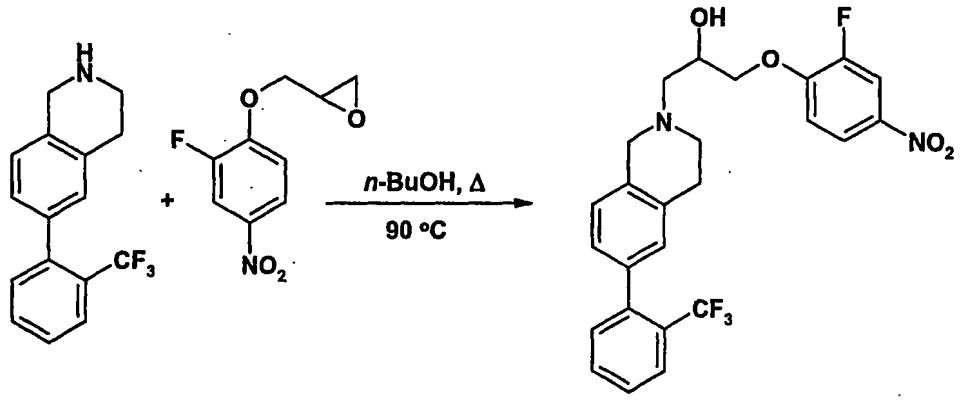
Compound 6e: 1,2,3,4-Tetrahydro-6-[2-(trifluoromethyl)phenyl]isoquinoline and 1,2,3,4-tetrahydro-8-[2-(trifluoromethyl)phenyl]isoquinoline



Following General Procedure 1, a mixture of 6-bromo-1,2,3,4-tetrahydro-2-(trifluoroacetyl)isoquinoline and 8-bromo-1,2,3,4-tetrahydro-2-(trifluoroacetyl)-isoquinoline (0.137 g, 0.446 mmol) was reacted with [2-(trifluoromethyl)phenyl]-boronic acid (0.127 g, 0.668 mmol) to provide a mixture of the title compounds. Purification by column chromatography (4:1 CH_2Cl_2:MeOH + 0.1% conc. NH_3) provided 1,2,3,4-tetrahydro-8-[2-(trifluoromethyl)phenyl]isoquinoline (0.0380 g, 31%) and 1,2,3,4-tetrahydro-6-[2-(trifluoromethyl)phenyl]isoquinoline (0.0810 g, 65%).

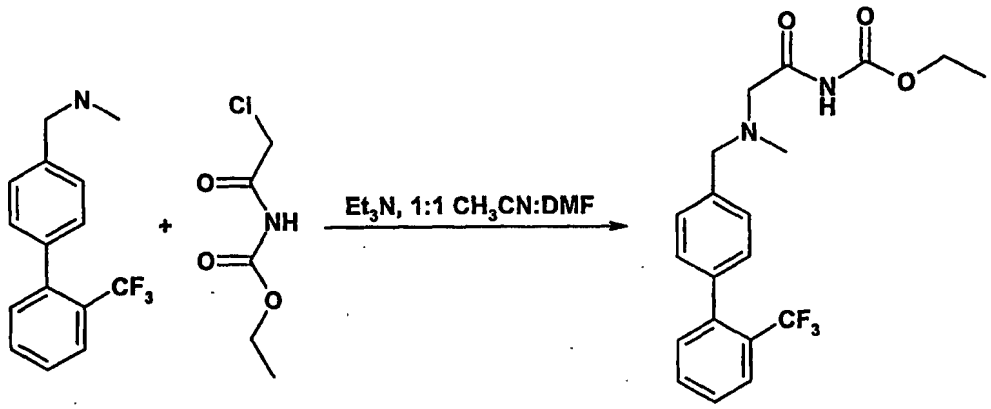
1,2,3,4-tetrahydro-8-[2-(trifluoromethyl)phenyl]isoquinoline: ^{1}H-NMR ($CDCl_3$): δ 7.77 (d, *J*=7.2 Hz, 1H), 7.56 (t, *J*=7.6 Hz, 1H), 7.49 (t, *J*=7.6 Hz, 1H), 7.23 (d, *J*=7.6 Hz, 1H), 7.21 (t, *J*=7.6 Hz, 1H), 7.16 (d, *J*=6.8 Hz, 1H), 7.01 (d, *J*=7.6 Hz, 1H), 4.66 (br s, 1H), 3.72 (half of br AB_q, *J*=16.0 Hz, 1H), 3.57 (half of br AB_q, *J*=15.6 Hz, 1H), 3.19 (br s, 2H), 2.97 (br s, 2H). MS (ESI) $(M+H)^+ = 278$.
1,2,3,4-tetrahydro-6-[2-(trifluoromethyl)phenyl]isoquinoline: ^{1}H-NMR ($CDCl_3$): δ 7.74 (d, *J*=7.6 Hz, 1H), 7.55 (t, *J*=6.8 Hz, 1H), 7.45 (t, *J*=8.0 Hz, 1H), 7.31 (d, *J*=7.6 Hz, 1H), 7.12 (d, *J*=8.4 Hz, 1H), 7.07 (s, 1H), 7.06 (d, *J*=8.0 Hz, 1H), 4.12 (br s, 2H), 3.87 (br s, 1H), 3.23 (br s, 2H), 2.88 (br s, 2H). MS (ESI) $(M+H)^+ = 278$.

Compound 6f: α-[(2-Fluoro-4-nitrophenoxy)methyl]-3,4-dihydro-6-[2-(trifluoromethyl)phenyl]-2(1*H*)-isoquinolineethanol



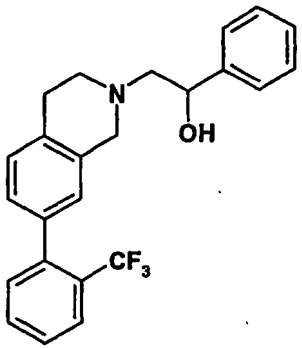
Following General Procedure 5, 1,2,3,4-tetrahydro-6-[2-(trifluoromethyl)phenyl]-isoquinoline (0.0256 g, 0.0923 mmol) and 2-[(2-fluoro-4-nitrophenoxy)methyl]-oxirane (0.0197 g, 0.0924 mmol) were combined and heated at 90 °C for 16 h. The crude product was purified by reverse phase HPLC (gradient 20-60% CH_3CN in H_2O) to provide the title compound (0.0222 g, 40%) as its TFA salt. This material was lyophilized from H_2O/acetonitrile to produce a white, hygroscopic solid. Due to quaternization of the stereogenic nitrogen atom, a mixture of 2 diastereomeric salts was obtained. ^{1}H-NMR (CD_3OD): δ 8.15-8.11 (m, 1H), 8.08 (dd, *J*=2.8 Hz, *J*=11.2 Hz, 1H), 7.79 (d, *J*=8.0 Hz, 1H), 7.66 (t, *J*=7.6 Hz, 1H), 7.57 (t, *J*=7.6 Hz, 1H), 7.39-7.24 (m, 5H), 4.82-4.50 (br m, 3H), 4.29 (d, *J*=4.8 Hz, 2H), 3.95 (br s, 1H), 3.62-3.52 (m, 3H), 3.38-3.22 (br m, 2H). MS (ESI) $(M+H)^+ = 491$. Anal. Calcd for $C_{25}H_{22}F_4N_2O_4$+1.1 TFA+0.7 H_2O: C, 51.98; H, 3.93; N, 4.46. Found: C, 52.02; H, 3.93; N, 4.42.

Example 7: Ethyl [[methyl-[[2'-(trifluoromethyl)-[1,1'-biphenyl]-4-yl]methyl]amino]-acetyl]carbamate

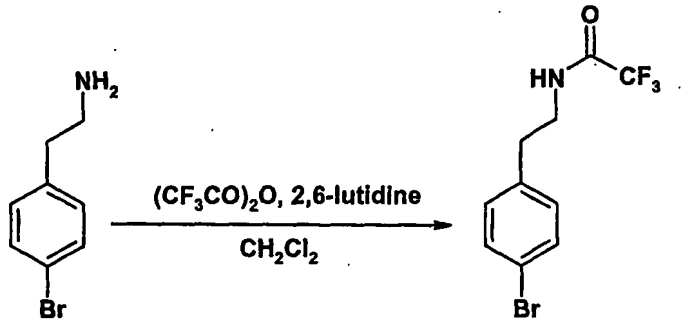


A mixture of N-methyl-2'-(trifluoromethyl)-[1,1'-biphenyl]-4-methanamine (0.0781 g, 0.294 mmol), ethyl N-(chloroacetyl)carbamate (0.0487 g, 0.294 mmol), and triethylamine (0.041 mL, 0.29 mmol) in 1:1 CH_3CN:DMF (3 mL) was stirred at room temperature for 24 h. The reaction mixture was concentrated, and the residue was partitioned between CH_2Cl_2 (5 mL) and H_2O (5 mL). The phases were separated, and the aqueous phase was extracted with CH_2Cl_2 (3 x 5 mL). The combined organic phases were dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The crude product was purified by reverse phase HPLC (gradient 20-60% CH_3CN in H_2O) to provide the title compound (0.0992 g, 86%) as its TFA salt. This material was lyophilized from H_2O/acetonitrile. ^{1}H-NMR (CD_3OD): δ 7.81 (d, *J*=8.0 Hz, 1H), 7.68 (t, *J*=7.6 Hz, 1H), 7.63 (d, *J*=8.0 Hz, 2H), 7.59 (t, *J*=8.0 Hz, 1H), 7.46 (d, *J*=8.0 Hz, 2H), 7.38 (d, *J*=7.6 Hz, 1H), 4.70-4.30 (br, 3H), 4.24 (q, *J*=7.2 Hz, 2H), 2.95 (s, 3H), 1.31 (t, *J*=7.2 Hz, 3H). MS (ESI) $(M+H)^+$ = 395. Anal. Calcd for $C_{20}H_{21}F_3N_2O_3$+1.3 TFA+0.4 H_2O: C, 49.37; H, 4.23; N, 5.09. Found: C, 49.45; H, 4.23; N, 5.05.

Example 8: 3,4-Dihydro-α-phenyl-7-[2-(trifluoromethyl)phenyl]-2(1*H*)-isoquinolineethanol

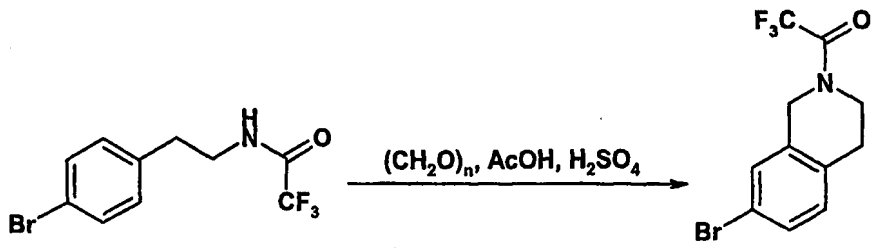


Compound 8a: *N*-[2-(4-Bromophenyl)ethyl]-2,2,2-trifluoroacetamide



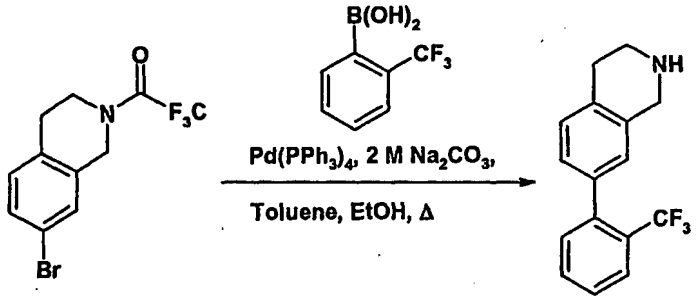
A mixture of 4-bromobenzeneethanamine (1.23 g, 6.17 mmol) and 2,6-lutidine (0.76 mL, 6.5 mmol) in dry CH_2Cl_2 (25 mL) was cooled to 0 °C. Trifluoroacetic anhydride (0.87 mL, 6.2 mmol) was added dropwise, and the reaction was then warmed to room temperature and allowed to stir for 16 h. Water (25 mL) was added to the reaction, the phases were separated, and the aqueous layer was extracted with CH_2Cl_2 (2 x 25 mL). The combined organic phases were washed successively with 1 M HCl (25 mL) and saturated $NaHCO_3$ (25 mL), and then dried over Na_2SO_4, filtered, and concentrated *in vacuo* to provide the title compound (1.79 g, 98%). The crude compound was used in subsequent steps. ^{1}H-NMR ($CDCl_3$): δ 7.49-7.45 (m, 2H), 7.10-7.06 (m, 2H), 6.27 (br s, 1H), 3.61 (q, *J*=6.8 Hz, 2H), 2.86 (t, *J*=6.8 Hz, 2H). MS (ESI) $(M+H)^+$ = 296/298.

Compound 8b: 7-Bromo-1,2,3,4-tetrahydro-2-(trifluoroacetyl)isoquinoline



A mixture of glacial acetic acid (5.1 mL) and concentrated sulfuric acid (3.4 mL) was added to a mixture of *N*-[2-(4-bromophenyl)ethyl]-2,2,2-trifluoroacetamide (0.903 g, 3.05 mmol) and paraformaldehyde (0.147 g, 4.88 mmol equiv. of formaldehyde). The reaction was stirred at room temperature for 20 h, and then poured into 65 mL of cold water. The aqueous solution was extracted with EtOAc (3 x 25 mL). The combined organic phases were washed with saturated $NaHCO_3$ (16 mL) and water (2 x 35 mL), and then dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The residue was purified by column chromatography (4:1 Hexanes:EtOAc) to provide the title compound (0.885 g, 94%) as a colorless oil. Due to hindered rotation about the amide bond, rotamers were observed in the ^{1}H-NMR spectrum. ^{1}H-NMR ($CDCl_3$): δ 7.38-7.27 (m, 2H), 7.06 (d, *J*=9.6 Hz, 0.36H), 7.04 (d, *J*=8.4 Hz, 0.64H), 4.76 (s, 1.3H), 4.71 (s, 0.7H), 3.88 (t, *J*=6.4 Hz, 0.7H), 3.84 (t, *J*=6.4 Hz, 1.3H), 2.91 (t, *J*=5.6 Hz, 1.3H), 2.90 (t, *J*=6.4 Hz, 0.7H). MS (ESI) $(M+H)^+$ = 308/310.

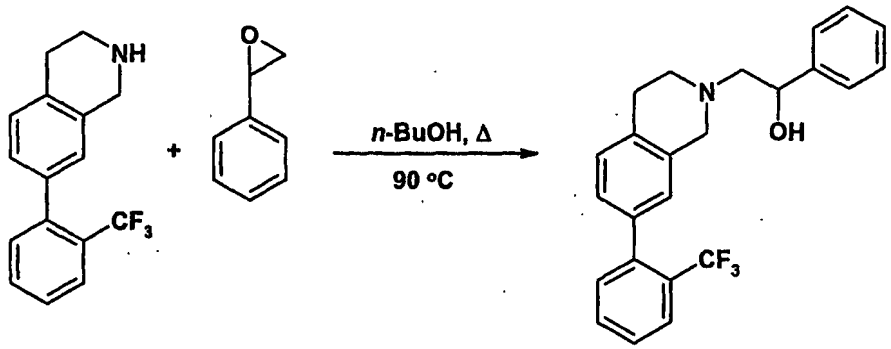
Compound 8c: 1,2,3,4-Tetrahydro-7-[2-(trifluoromethyl)phenyl]isoquinoline



Following General Procedure 1, 7-bromo-1,2,3,4-tetrahydro-2-(trifluoroacetyl)isoquinoline (0.468 g, 1.52 mmol) was reacted with [2-(trifluoromethyl)phenyl]boronic acid (0.433 g, 2.28 mmol) to provide the title compound (0.387 g, 92%) following purification by column chromatography (85:15 CH_2Cl_2:MeOH + 0.1% conc. NH_3). ^{1}H-NMR ($CDCl_3$): δ 7.74 (d, *J*=8.0 Hz, 1H), 7.54

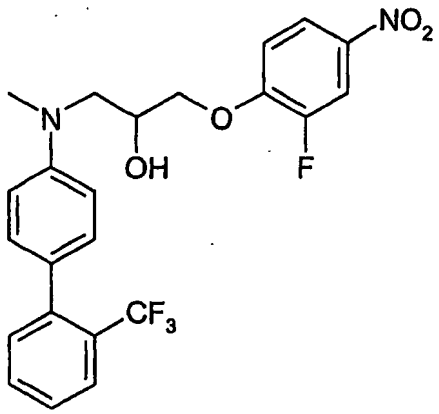
(t, *J*=7.6 Hz, 1H), 7.45 (t, *J*=8.0 Hz, 1H), 7.31 (d, *J*=7.6 Hz, 1H), 7.12 (collapsed AB_q, 2H), 6.99 (s, 1H), 4.05 (s, 2H), 3.20 (t, *J*=5.6 Hz, 2H), 2.86 (t, *J*=6.0 Hz, 2H), 2.43 (br s, 1H). MS (ESI) $(M+H)^+ = 278$.

Compound 8d: 3,4-Dihydro-α-phenyl-7-[2-(trifluoromethyl)phenyl]-2(1*H*)-isoquinolineethanol

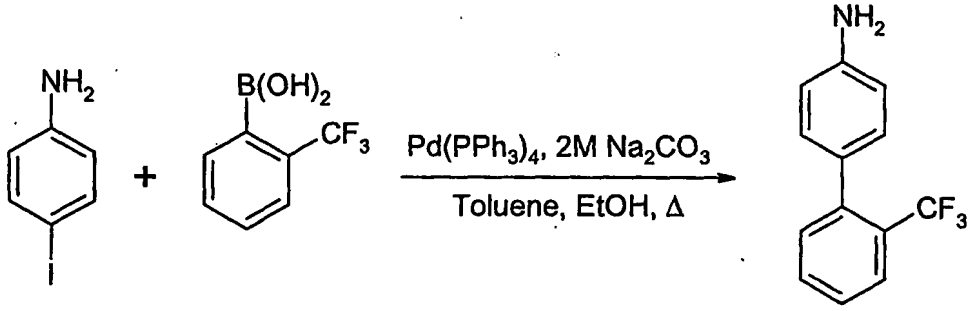


Following General Procedure 5, 1,2,3,4-tetrahydro-7-[2-(trifluoromethyl)phenyl]-isoquinoline (0.0509 g, 0.184 mmol) and 2-(phenyl)oxirane (0.021 mL, 0.0877 mmol) were combined and heated at 90 °C for 14 h. The crude product was purified by reverse phase HPLC (gradient 20-60% CH_3CN in H_2O) to provide the title compound (0.0138 g, 15%) as its TFA salt. This material was lyophilized from H_2O/acetonitrile to produce a white, hygroscopic solid. Due to quaternization of the stereogenic nitrogen atom, a mixture of 2 diastereomeric salts was obtained. ^{1}H-NMR (CD_3OD): δ 7.80 (d, *J*=8.0 Hz, 1H), 7.67 (t, *J*=7.6 Hz, 1H), 7.57 (t, *J*=7.6 Hz, 1H), 7.53-7.47 (m, 2H), 7.44-7.32 (m, 5H), 7.29 (d, *J*=8.4 Hz, 1H), 7.27-7.14 (br m, 1H), 5.25 (dd, *J*=3.6 Hz, *J*=10.4 Hz, 1H), 4.88-4.43 (br m, 2H), 4.13-3.90 (br m, 1H), 3.62-3.14 (br m, 5H). MS (ESI) $(M+H)^+ = 398$. Anal. Calcd for $C_{24}H_{22}F_3NO$+1.1 TFA: C, 60.19; H, 4.45; N, 2.68. Found: C, 60.16; H, 4.38; N, 2.61.

Example 9: 1-(2-Fluoro-4-nitrophenoxy)-3-[methyl[2'-(trifluoromethyl)[1,1'-biphenyl]-4-yl]amino]- 2-propanol

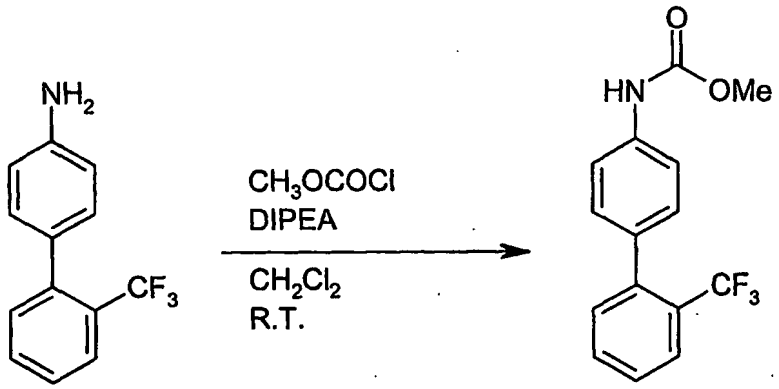


Compound 9a: 2'-(Trifluoromethyl)- [1,1'-biphenyl]-4-amine



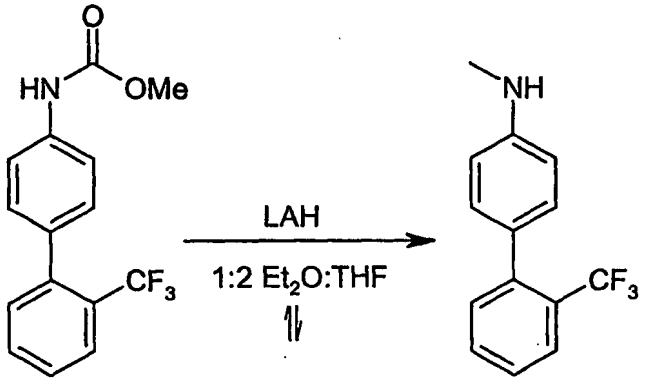
Following General Procedure 1, 4-iodoaniline(1.00 g, 4.57 mmol), 2-(trifluoromethyl)phenylboronic acid (1.302 g, 6.86 mmol), $Pd(PPh_3)_4$ (0.265 g, 0.23 mmol), and 2 M Na_2CO_3 (16 mL, 32 mmol) were combined. Following the usual work-up, silica gel column chromatography (9:1 Hexanes:EtOAc) provided the title compound (0.476 g, 44%). ^{1}H-NMR ($CDCl_3$): δ 7.71 (dd, *J*=0.4 Hz, *J*=7.8 Hz, 1H), 7.52 (t, *J*=7.4 Hz, 1H), 7.41 (t, *J*=7.8 Hz, 1H), 7.32 (dd, *J*=0.4 Hz, *J*=7.6 Hz, 1H), 7.12 (d, *J*=8.2 Hz, 1H), 6.73-6.69 (m, 2H), 3.73 (br s, 2H). MS (ESI) $(M+H)^+ = 238$.

Compound 9b: Methyl [2'-(trifluoromethyl)[1,1'-biphenyl]-4-yl]carbamate



To a solution of 2'-(trifluoromethyl)- [1,1'-biphenyl]-4-amine (0.476 g, 2.01 mmol) and DIPEA (0.45 mL, 2.61 mmol) in CH_2Cl_2 (4.5 mL) maintained at 0 °C was added methylchloroformate (0.17 mL, 2.21 mmol). The reaction was allowed to slowly warm to room temperature, stirred overnight, diluted with CH_2Cl_2 (15 mL), and washed with 1 N HCl (2 x 20 mL) and brine (1 x 20 mL). The organic layer was then dried over Na_2SO_4, filtered, and concentrated *in vacuo* to provide the title compound (0.563 g, 95%) as a beige solid. ^{1}H-NMR ($CDCl_3$): δ 7.74 (dd, *J*=0.6 Hz, *J*=7.8 Hz, 1H), 7.50 (t, *J*=7.8 Hz, 1H), 7.47-7.42 (overlapping d and t, *J*=8.0 Hz for d and *J*=8.4 Hz for t, 3H), 7.32 (d, *J*=8.0 Hz, 1H), 7.28 (d, *J*=8.4 Hz, 2H), 6.69 (br s, 1H), 3.80 (s, 3H). MS (ESI) $(M+H)^+ = 296$.

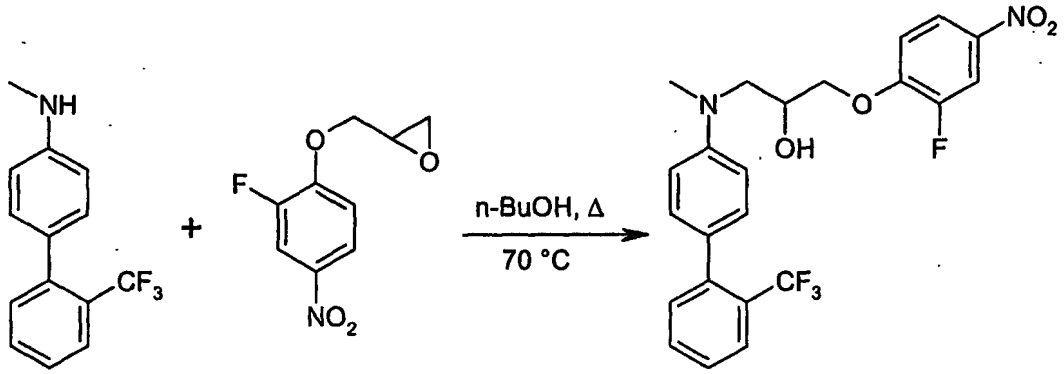
Compound 9c: N-Methyl-2'-(trifluoromethyl)-[1,1'-biphenyl]-4-amine



To a solution of methyl [2'-(trifluoromethyl)[1,1'-biphenyl]-4-yl]carbamate (0.554 g, 1.88 mmol) in 1:2 dry Et_2O:THF (30 mL) was added LAH in Et_2O (2.82 mL, 2.82 mmol) dropwise. The reaction was refluxed for 4 hrs, cooled down to room

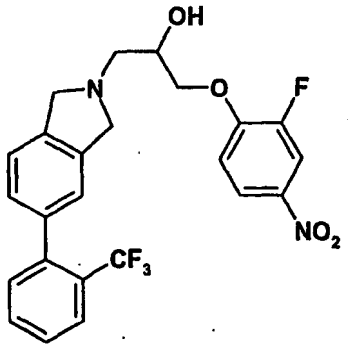
temperature, diluted with Et_2O (40 mL), and quenched with $Na_2SO_4 \cdot 5H_2O$ (2 g). The reaction mixture was stirred until the solution turned clear, filtered, and concentrated *in vacuo* to provide the title compound (0.409 g, 87%) as a yellow oil. ^{1}H-NMR ($CDCl_3$): δ 7.71 (d, *J*=8.2 Hz, 1H), 7.52 (t, *J*=7.6 Hz, 1H), 7.40 (t, *J*=7.6 Hz, 1H), 7.33 (d, *J*=7.4 Hz, 1H), 7.17 (d, *J*=8.2 Hz, 2H), 6.64 (d, *J*=8.8 Hz, 2H), 2.88 (s, 3H). MS (ESI) $(M+H)^+ = 252$.

Compound 9d: 1-(2-Fluoro-4-nitrophenoxy)-3-[methyl[2'-(trifluoromethyl)[1,1'-biphenyl]-4-yl]amino]- 2-propanol

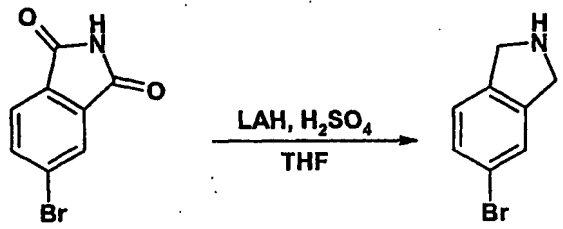


Following General Procedure 5, N-methyl-2'-(trifluoromethyl)-[1,1'-biphenyl]-4-amine (0.100 g, 0.40 mmol) and 2-[(2-fluoro-4-nitrophenoxy)methyl]oxirane (0.085 g, 0.33 mmol) were combined and heated at 70 °C for 24 h. The crude product was purified by reverse phase HPLC (gradient 40-80% CH_3CN in H_2O) to provide the title compound (0.077 g, 42%) as its TFA salt. This material was lyophilized from H_2O/ CH_3CN to produce a yellow solid. ^{1}H-NMR (CD_3OD): δ 8.07-8.02 (m, 2H), 7.71 (d, *J*=7.6 Hz, 1H), 7.57 (t, *J*=7.4 Hz, 1H), 7.46 (t, *J*=7.6 Hz, 1H), 7.29-7.49 (m, 4H), 7.03 (br d, *J*=7.6 Hz, 2H), 4.24-4.14 (m, 3H), 3.79 (dd, *J*=5.0 Hz, *J*=14.2 Hz, 1H), 3.57 (dd, *J*=7.2 Hz, *J*=14.4 Hz, 1H), 3.14 (s, 3H). MS (ESI) $(M+H)^+ = 465$. Anal. Calcd for $C_{23}H_{20}F_4N_2O_4 + 0.2\ H_2O + 0.3$ TFA: C, 56.44; H, 4.15; N, 5.58. Found: C, 56.41; H, 4.05; N, 5.53.

Example 10: α-[(2-Fluoro-4-nitrophenoxy)methyl]-1,3-dihydro-5-[2-(trifluoromethyl)phenyl]-2*H*-isoindole-2-ethanol

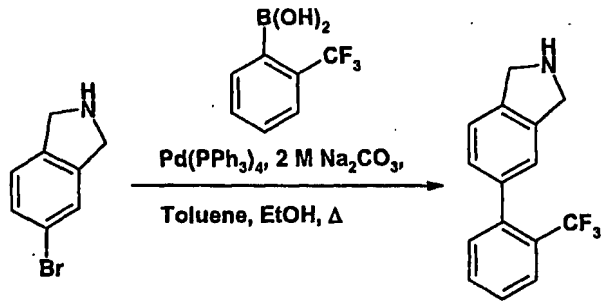


Compound 10a: 5-Bromo-2,3-dihydro-1*H*-isoindole



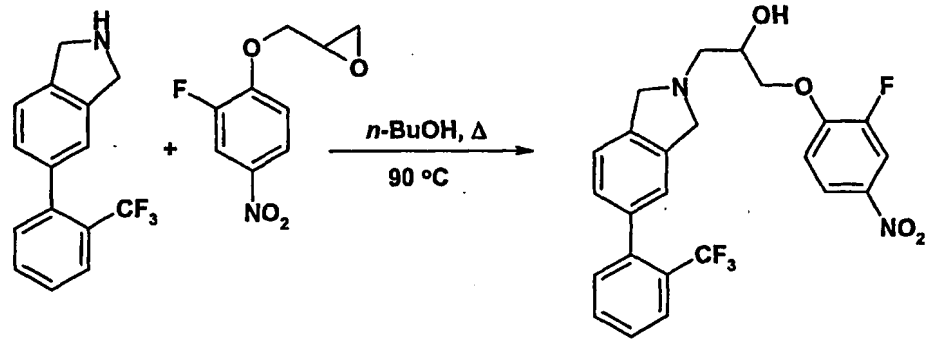
A solution of $LiAlH_4$ (8.8 mL of 1 M solution in Et_2O, 8.8 mmol) in dry THF (13 mL) was cooled to 0 °C. Concentrated H_2SO_4 (0.42 g, 4.3 mmol) was added dropwise, and the resulting mixture was stirred at 0 °C for 30 min. 5-Bromo-1*H*-isoindole-1,3(2*H*)-dione (0.409 g, 1.81 mmol) was added in portions over 15 minutes, and the reaction was allowed to warm to room temperature when the addition was complete. The reaction was stirred at room temperature for 2.5h, and then cooled back to 0 °C and quenched by the addition of MeOH (2 mL). Et_2O was added (50 mL), followed by $Na_2SO_4 \cdot 10H_2O$. The mixture was stirred vigorously until the organic layer was clear. The mixture was then filtered and concentrated *in vacuo*. Purification by column chromatography (4:1 CH_2Cl_2:MeOH + 0.1% conc. NH_3) provided the title compound (0.128 g, 36%). ^{1}H-NMR ($CDCl_3$): δ 7.38 (s 1H), 7.33 (d, *J*=7.6 Hz, 1H), 7.12 (d, *J*=8.0 Hz, 1H), 4.21 (s, 2H), 4.17 (s, 2H), 2.09 (s, 1H). MS (ESI) $(M+H)^+$ = 198/200.

Compound 10b: 2,3-Dihydro-5-[2-(trifluoromethyl)phenyl]-1*H*-isoindole



Following General Procedure 1, 5-bromo-2,3-dihydro-1*H*-isoindole (0.128 g, 0.647 mmol) was reacted with [2-(trifluoromethyl)phenyl]boronic acid (0.184 g, 0.971 mmol) to provide the title compound (0.124 g, 73%) following purification by column chromatography (85:15 CH_2Cl_2:MeOH + 0.1% conc. NH_3). ^{1}H-NMR ($CDCl_3$): δ 7.74 (d, *J*=8.0 Hz, 1H), 7.55 (t, *J*=8.4 Hz, 1H), 7.46 (t, *J*=7.6 Hz, 1H), 7.32 (d, *J*=7.2 Hz, 1H), 7.28 (d, *J*=7.6 Hz, 1H), 7.21 (s, 1H), 7.17 (d, *J*=8.0 Hz, 1H), 4.30 (s, 2H), 4.29 (s, 2H), 2.34 (br s, 1H). MS (ESI) $(M+H)^+$ = 264.

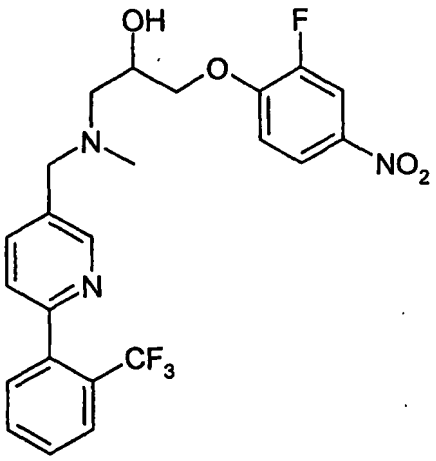
Compound 10c: α-[(2-Fluoro-4-nitrophenoxy)methyl]-1,3-dihydro-5-[2-(trifluoromethyl)phenyl]-2*H*-isoindole-2-ethanol



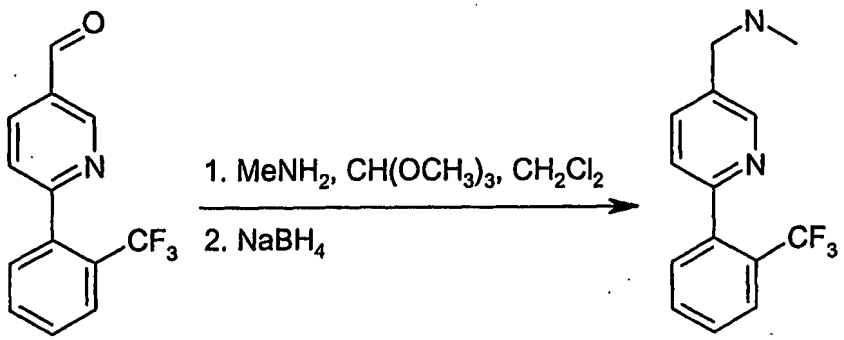
Following General Procedure 5, 2,3-dihydro-5-[2-(trifluoromethyl)phenyl]-1*H*-isoindole (0.0585 g, 0.222 mmol) and 2-[(2-fluoro-4-nitrophenoxy)methyl]-oxirane (0.0474 g, 0.222 mmol) were combined and heated at 90 °C for 14 h. The crude product was purified by reverse phase HPLC (gradient 20-65% CH_3CN in H_2O) to provide the title compound (0.0374 g, 29%) as its TFA salt. This material was lyophilized from H_2O/acetonitrile to produce a white, hygroscopic solid. Due to quaternization of the stereogenic nitrogen atom, a mixture of 2 diastereomeric salts was obtained. ^{1}H-NMR (CD_3OD): δ 8.13 (ddd, *J*=1.6 Hz, *J*=2.8 Hz, *J*=9.2 Hz, 1H),

8.09 (dd, *J*=2.8 Hz, *J*=11.2 Hz, 1H), 7.81 (d, *J*=7.6 Hz, 1H), 7.68 (t, *J*=7.2 Hz, 1H), 7.59 (t, *J*=7.6 Hz, 1H), 7.50 (d, *J*=8.0 Hz, 1H), 7.42-7.33 (m, 4H), 5.08-4.74 (br s, 4H), 4.52 (sextet, *J*=4.8 Hz, 1H), 4.30 (d, *J*=4.8 Hz, 2H), 3.79-3.68 (m, 2H). MS (ESI) $(M+H)^+ = 477$. Anal. Calcd for $C_{24}H_{20}F_4N_2O_4$+0.6 TFA+2.5 H_2O: C, 51.31; H, 4.37; N, 4.75. Found: C, 51.29; H, 4.38; N, 4.54.

Example 11: 1-(2-Fluoro-4-nitrophenoxy)-3-[methyl[[6-[2-(trifluoromethyl)phenyl]-3-pyridinyl]methyl]amino]- 2-propanol



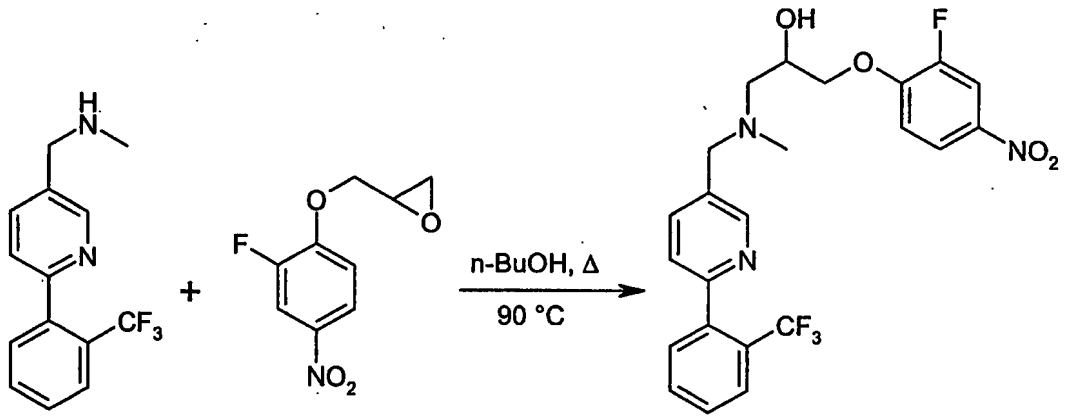
Compound 11a: *N*-Methyl-6-[2-(trifluoromethyl)phenyl]-3-pyridinemethanamine



6-[2-(Trifluoromethyl)phenyl]-3-pyridinecarboxaldehyde (0.360 g, 1.43 mmol) was treated according to General Procedure 3 to provide the title compound (0.312 g, 91%). The crude material was of sufficient purity (>90%) to be used in subsequent steps. ^{1}H-NMR ($CDCl_3$): δ 8.62 (d, *J*=1.6 Hz, 1H), 7.76 (d, *J*=7.6 Hz, 1H), 7.73 (d,

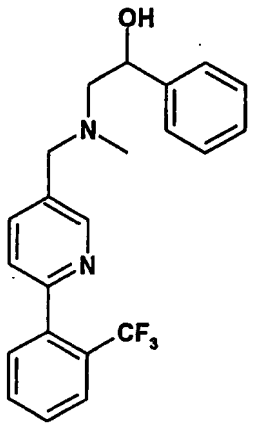
J=2.0 Hz, 1H), 7.61 (t, *J*=7.6 Hz, 1H), 7.54-7.48 (m, 2H), 7.40 (d, *J*=8.0 Hz, 1H), 3.84 (s, 2H), 2.50 (s, 3H). MS (ESI) $(M+H)^+ = 267$.

Compound 11b: 1-(2-Fluoro-4-nitrophenoxy)-3-[methyl[[6-[2-(trifluoromethyl)phenyl]-3-pyridinyl]methyl]amino]- 2-propanol

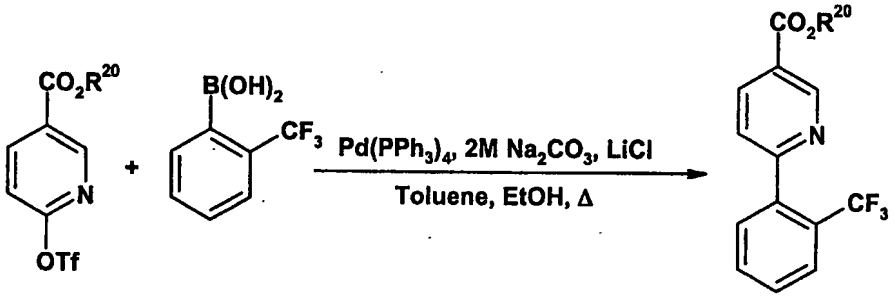


Following General Procedure 5, *N*-methyl-6-[2-(trifluoromethyl)phenyl]-3-pyridinemethanamine (0.100 g, 0.38 mmol) and 2-[(2-fluoro-4-nitrophenoxy)methyl]oxirane (0.094 g, 0.38 mmol) were combined and heated at 90 °C for 24 h. The crude product was purified by reverse phase HPLC (gradient 20-50% CH_3CN in H_2O) to provide the title compound (0.071 g, 31%) as its TFA salt. This material was lyophilized from H_2O/ CH_3CN to produce a white solid. ^{1}H-NMR (CD_3OD): δ 8.78 (d, *J*=1.6 Hz, 1H), 8.13-8.03 (m, 3H), 7.84 (d, *J*=7.6 Hz, 1H), 7.74 (t, *J*=7.2 Hz, 1H), 7.67 (d, *J*=8.0 Hz, 1H), 7.64 (d, *J*=8.0 Hz, 1H), 7.51 (d, *J*=7.6 Hz, 1H), 7.30 (t, *J*=8.6 Hz, 1H), 4.66 (br s, 1H), 4.53 (br s, 2H), 4.23 (d, *J*=4.8 Hz, 2H), 3.43 (t, *J*=10.0 Hz, 2H), 2.99 (s, 3H). MS (ESI) $(M+H)^+ = 480$. Anal. Calcd for $C_{23}H_{21}F_4N_3O_4 + 0.8\ H_2O + 1.2$ TFA: C, 48.37; H, 3.80; N, 6.66. Found: C, 48.37; H, 3.70; N, 6.79.

Example 12: α-[[Methyl-[[6-[2-(trifluoromethyl)phenyl]-3-pyridinyl]methyl]amino]methyl]-benzenemethanol



Compound 12a: Methyl 6-[2-(trifluoromethyl)phenyl]-3-pyridinecarboxylate and Ethyl 6-[2-(trifluoromethyl)phenyl]-3-pyridinecarboxylate

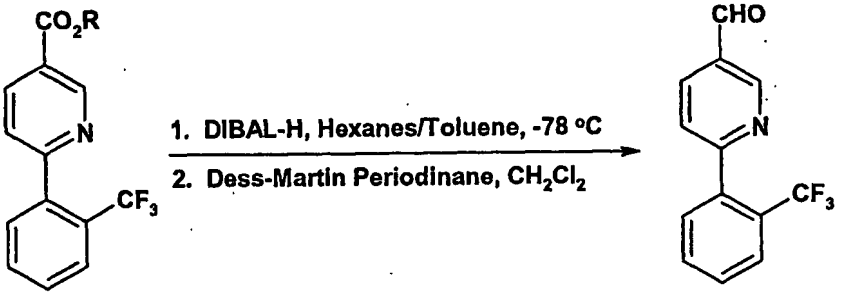


R^{20} = Methyl, or Ethyl

A solution of [2-(trifluoromethyl)phenyl]boronic acid (2.27 g, 12.0 mmol) in ethanol (30 mL) was added to a mixture of methyl 6-[[(trifluoromethyl)sulfonyl]oxy]-3-pyridinecarboxylate (2.27 g, 7.96 mmol), LiCl (1.01 g, 23.9 mmol), $Pd(PPh_3)_4$ (0.46 g, 0.40 mmol), toluene (120 mL), and 2 M Na_2CO_3 (12 mL). The resulting mixture was heated at reflux for 18 h. The reaction was then concentrated *in vacuo*, and the residue was diluted with water (60 mL). The aqueous phase was extracted with EtOAc (3 x 60 mL). The combined organic phases were then washed with brine (80 mL), dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The residue was purified by column chromatography (4:1 Hexanes:EtOAc) to provide the title compound as a 1:1.4 mixture of the methyl and ethyl esters (1.59 g, 69%). Methyl

ester: ^{1}H-NMR ($CDCl_3$): δ 9.30 (dd, *J*=0.8 Hz, *J*=2.0 Hz, 1H), 8.37 (dd, *J*=2.4 Hz, *J*=7.2 Hz, 1H), 7.80 (dd, *J*=0.8 Hz, *J*=8.0 Hz, 1H), 7.65 (t, *J*=7.6 Hz, 1H), 7.67-7.50 (m, 3H), 4.00 (s, 3H). MS (ESI) $(M+H)^+$ = 282. Ethyl ester: ^{1}H-NMR ($CDCl_3$): δ 9.29 (dd, *J*=0.8 Hz, *J*=2.4 Hz, 1H), 8.37 (dd, *J*=2.4 Hz, *J*=8.4 Hz, 1H), 7.79 (dd, *J*=0.8 Hz, *J*=8.4 Hz, 1H), 7.65 (t, *J*=7.6 Hz, 1H), 7.60-7.50 (m, 3H), 4.45 (q, *J*=7.2 Hz, 2H), 1.44 (t, *J*=7.2 Hz, 3H). MS (ESI) $(M+H)^+$ = 296.

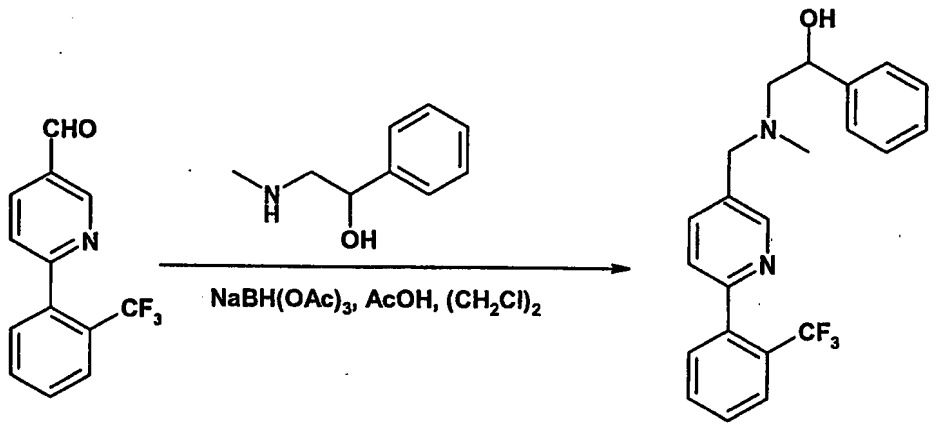
Compound 12b: 6-[2-(Trifluoromethyl)phenyl]-3-pyridinecarboxaldehyde



DIBAL-H (12.1 mL of a 1 M solution in hexanes, 12.1 mmol) was added dropwise to a solution of a mixture of methyl and ethyl 6-[2-(trifluoromethyl)phenyl]-3-pyridinecarboxylate (1.59 g of a 1:1.4 mixture, 5.50 mmol) in dry toluene (45 mL) maintained at –78 °C. After the addition was complete, the reaction was stirred at –78 °C for 30 min, and then 12 mL of 1 N HCl was added cautiously and the mixture was allowed to warm to room temperature. Additional water (30 mL) was added, the layers were separated, and the aqueous phase was extracted with EtOAc (3 x 60 mL). The combined organic phases were then dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The residue was dissolved in CH_2Cl_2 (50 mL) and Dess-Martin periodinane (2.36 g, 5.57 mmol) was added in portions. After the addition was complete, the reaction was stirred at room temperature for 2 h. The reaction was then quenched with 1:1 saturated $NaHCO_3$:saturated $Na_2S_2O_3$ (40 mL) and stirred for 15 min. The layers were separated, and the aqueous phase was extracted with CH_2Cl_2 (3 x 40 mL). The combined organic phases were then dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The residue was purified by column chromatography (3:2 Hexanes:EtOAc) to provide the title compound (1.23 g, 89% for the two steps) as a slightly yellow oil which solidified upon storage in the freezer. ^{1}H-NMR ($CDCl_3$): δ 10.19 (s, 1H), 9.16

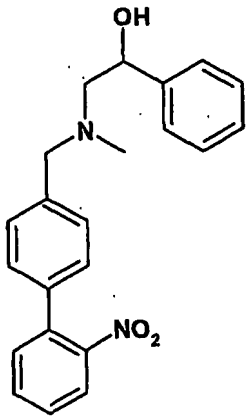
(dd, *J*=0.8 Hz, *J*=2.0 Hz, 1H), 8.25 (dd, *J*=2.4 Hz, *J*=8.0 Hz, 1H), 7.81 (d, *J*=8.0 Hz, 1H), 7.70-7.56 (m, 3H), 7.52 (d, *J*=7.6 Hz, 1H). MS (ESI) $(M+H)^+ = 252$.

Compound 12c: α-[[Methyl-[[6-[2-(trifluoromethyl)phenyl]-3-pyridinyl]methyl]amino]methyl]-benzenemethanol

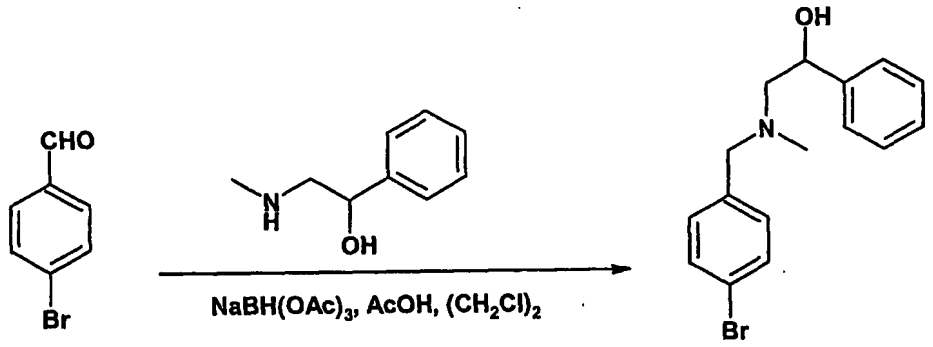


Following General Procedure 4, 6-[2-(trifluoromethyl)phenyl]-3-pyridine-carboxaldehyde (0.166 g, 0.66 mmol), α-[(methylamino)methyl]benzenemethanol (0.100 g, 0.66 mmol), and $NaBH(OAc)_3$ (0.280 g, 1.32 mmol) were combined. The crude product was purified by reverse phase HPLC (gradient 20-40% CH_3CN in H_2O) to provide the title compound (0.279 g, 84%) as its TFA salt. This material was lyophilized from H_2O/acetonitrile to produce a white, hygroscopic solid. ^{1}H-NMR (CD_3OD): δ 8.81 (s, 1H), 8.14 (d, *J*=8.0 Hz, 1H), 7.86 (d, *J*=8.0 Hz, 1H), 7.57 (t, *J*=7.2 Hz, 1H), 7.72-7.64 (m, 2H), 7.55 (d, *J*=7.2 Hz, 1H), 7.48-7.31 (m, 5H), 5.17 (br m, 1H), 4.54 (br s, 2H), 3.33 (br s, 2H), 3.03 (br s, 3H). MS (ESI) $(M+H)^+ = 387$. Anal. Calcd for $C_{22}H_{21}F_3N_2O$+1.2 TFA+1.1 H_2O: C, 53.97; H, 4.53; N, 5.16. Found: C, 54.00; H, 4.43; N, 5.52.

Example 13: α-[[Methyl[(2'-nitro[1,1'-biphenyl]-4-yl)methyl]amino]methyl]-benzenemethanol

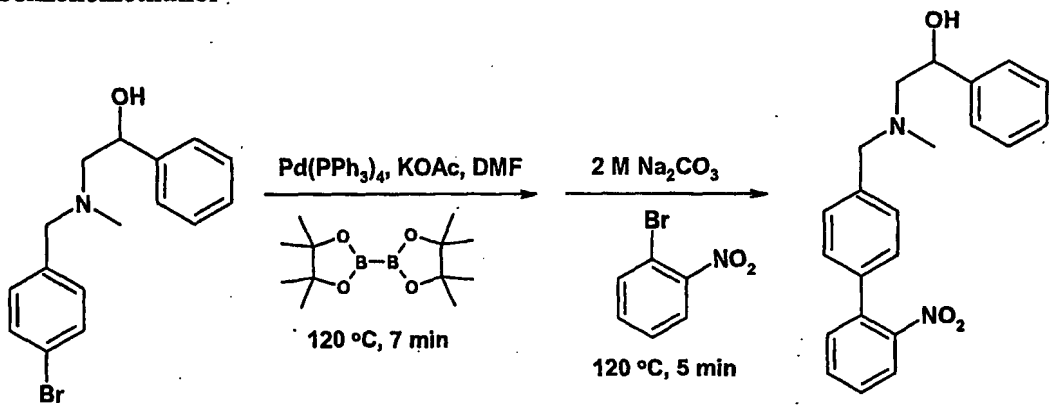


Compound 13a: α-[[[(4-Bromophenyl)methyl]methylamino]methyl] benzenemethanol



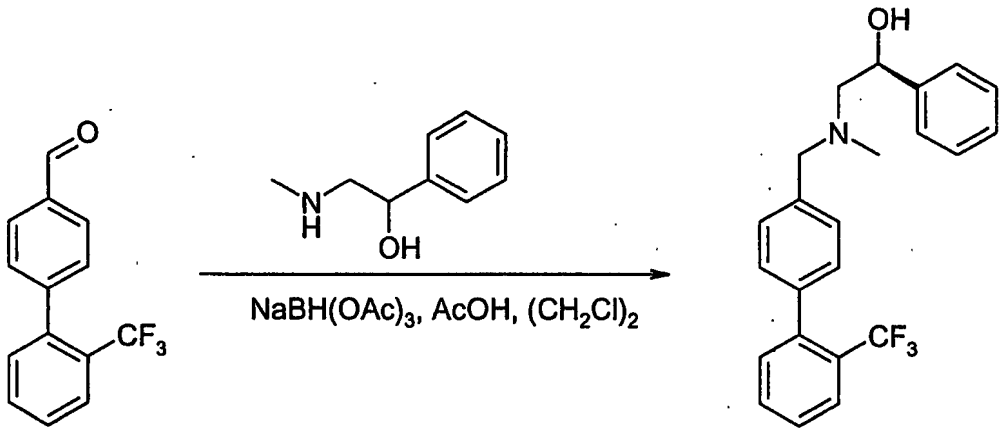
Following General Procedure 4, 4-bromobenzaldehyde (1.22 g, 6.59 mmol), α-[(methylamino)methyl]benzenemethanol (0.500 g, 3.31 mmol), and $NaBH(OAc)_3$ (1.40 g, 6.61 mmol) were combined. The crude product was purified by flash chromatography (Gradient of 100% CH_2Cl_2 to 9:1 CH_2Cl_2:MeOH + 0.1% conc. NH_3) to provide the title compound (0.942 g, 89%). ^{1}H-NMR (CD_3OD): δ 7.48-7.44 (m, 2H), 7.36-7.32 (m, 4H), 7.32-7.24 (m, 1H), 7.21-7.17 (m, 2H), 4.75 (dd, *J*=3.6 Hz, *J*=10.4 Hz, 1H), 3.69 (d, *J*=13.2 Hz, 1H), 3.48 (d, *J*=13.2 Hz, 1H), 2.59 (half of d of AB_q, *J*=10.4 Hz, *J*=12.4 Hz, 1H), 2.52 (half of d of AB_q, *J*=3.2 Hz, *J*=12.4 Hz, 1H), 2.31 (s, 3H). MS (ESI) $(M+H)^+$ = 320/322.

Compound 13b: α-[[Methyl[(2'-nitro[1,1'-biphenyl]-4-yl)methyl]amino]methyl]-benzenemethanol



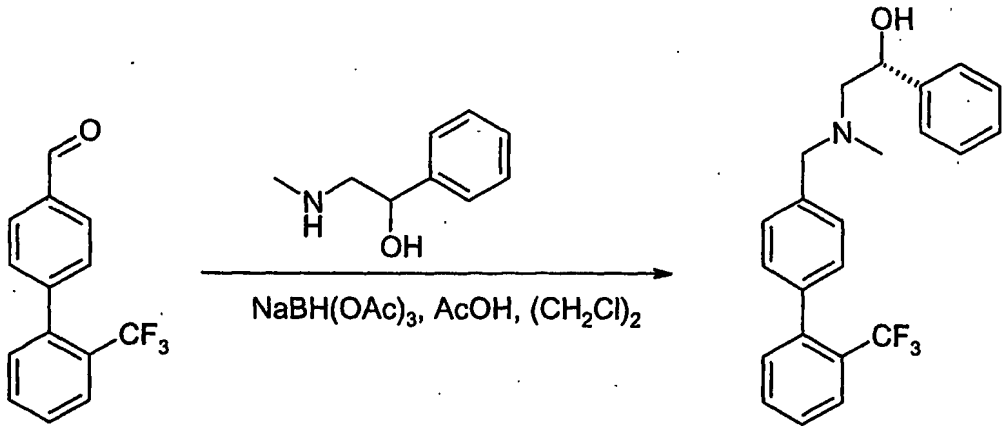
Following General Procedure 2, α-[[[(4-bromophenyl)methyl]methylamino]-methyl]benzenemethanol (0.0530 g, 0.165 mmol) and bis(pinacolato)diboron (0.0462 g, 0.182 mmol) were combined. The resulting boronate ester was used for the reaction with 1-bromo-2-nitrobenzene (0.0669 g, 0.331 mmol) as the second aryl halide. The crude product was purified by reverse phase HPLC (gradient 25-45% CH_3CN in H_2O) to provide the title compound (0.0113 g, 14%) as its TFA salt. This material was lyophilized from H_2O/acetonitrile to produce a white, hygroscopic solid. Due to quaternization of the stereogenic nitrogen atom, a mixture of 2 diastereomeric salts was obtained. ^{1}H-NMR (CD_3OD): δ 7.96 (d, *J*=8.0 Hz, 1H), 7.75 (t, *J*=7.2 Hz, 1H), 7.70-7.57 (br m, 3H), 7.57-7.29 (br m, 8H), 5.11 (dd, *J*=3.6 Hz, *J*=10.8 Hz, 1H), 4.75 (br d, *J*=12.8 Hz, 0.5H), 4.54-4.44 (br m, 1H), 4.32 (br d, *J*=12.0 Hz, 0.5H), 3.48-3.15 (br m, 2H), 3.07 (s, 1.5H), 2.91 (s, 1.5H). MS (ESI) $(M+H)^+$ = 363. Anal. Calcd for $C_{22}H_{22}N_2O_3$+1.1 TFA+1.1 H_2O: C, 57.25; H, 5.02; N, 5.52. Found: C, 57.26; H, 4.97; N, 5.46.

Example 14: (α^1S)-α-[[Methyl[[2'-(trifluoromethyl)[1,1'-biphenyl]-4-yl]methyl]amino]methyl]-benzenemethanol



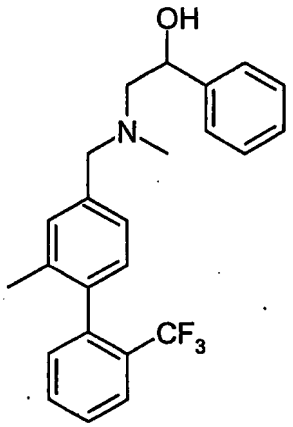
Following General Procedure 4, 2'-(trifluoromethyl)- [1,1'-biphenyl]-4-carboxaldehyde (0.375 g, 1.50 mmol), α-[(methylamino)methyl]benzenemethanol (0.453 g, 3.00 mmol), and $NaBH(OAc)_3$ (0.636 g, 3.00 mmol) were combined. Following the usual work-up, silica gel column chromatography (9:1 Hexanes:EtOAc) provided the title compound as a racemic mixture. Subsequent chromatography using CHIRALCEL®OD (990:10:1 EtOH:Hex:Et_2NH) gave the title compound. The HCl salt of the title compound (0.0102 g, 3%) was prepared using 1M HCl in Et_2O. This material was lyophilized to produce a white solid. Due to quaternization of the stereogenic nitrogen atom, a mixture of 2 diastereomeric salts was obtained. $[\alpha]_D^{24}$ = +44.2° (c=1.02, MeOH). ^{1}H-NMR (CD_3OD): δ 7.80 (d, *J*=7.6 Hz, 1H), 7.69-7.56 (overlapping t at 7.67 and m, *J*=7.4 Hz, 4H), 7.46-7.32 (overlapping d at 7.45 and br m, *J*=8.0 Hz, 8H), 5.11 (dd, *J*=6.8 Hz, *J*=7.2 Hz, 1H), 4.85-4.35 (br m, 2H), 3.26 (br s, 2H), 3.00 (br s, 3H). MS (ESI) $(M+H)^+$ = 386. Anal. Calcd for $C_{23}H_{22}F_3NO$ + 0.1 H_2O + 1.2 HCl: C, 64.10; H, 5.47; N, 3.25. Found: C, 64.15; H, 5.33; N, 3.80.

Example 15: (α^1R)-α-[[Methyl[[2'-(trifluoromethyl)[1,1'-biphenyl]-4-yl]methyl]amino]methyl]-benzenemethanol

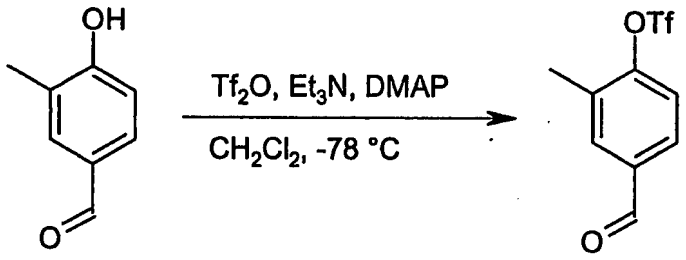


Following General Procedure 4, 2'-(trifluoromethyl)- [1,1'-biphenyl]-4-carboxaldehyde (0.375 g, 1.50 mmol), α-[(methylamino)methyl]benzenemethanol (0.453 g, 3.00 mmol), and $NaBH(OAc)_3$ (0.636 g, 3.00 mmol) were combined. Following the usual work-up, silica gel column chromatography (9:1 Hexanes:EtOAc) provided the title compound as a racemic mixture. Subsequent chromatography using CHIRALCEL®OD (990:10:1 EtOH:Hex:Et_2NH) gave the title compound. The HCl salt of the title compound (0.0056 g, 2%) was prepared using 1M HCl in Et_2O. This material was lyophilized to produce a white solid. Due to quaternization of the stereogenic nitrogen atom, a mixture of 2 diastereomeric salts was obtained. $[\alpha]_D^{28} = -49.5°$ (c=0.56, MeOH). ^{1}H-NMR (CD_3OD): δ 7.79 (d, *J*=8.0 Hz, 1H), 7.68-7.55 (overlapping t at 7.66 and m, *J*=7.6 Hz, 4H), 7.45-7.30 (overlapping d at 7.44 and br m, *J*=7.6 Hz, 8H), 5.10 (dd, *J*=6.4 Hz, *J*=7.6 Hz, 1H), 4.84-4.33 (br m, 2H), 3.25 (br s, 2H), 2.98 (br s, 3H). MS (ESI) $(M+H)^+ = 386$. Anal. Calcd for $C_{23}H_{22}F_3NO + 1.5$ HCl: C, 62.77; H, 5.38; N, 3.18. Found: C, 62.89; H, 5.31; N, 3.40.

Example 16: α-[[Methyl[[2-methyl-2'-(trifluoromethyl)[1,1'-biphenyl]-4-yl]methyl]amino]methyl]- benzenemethanol

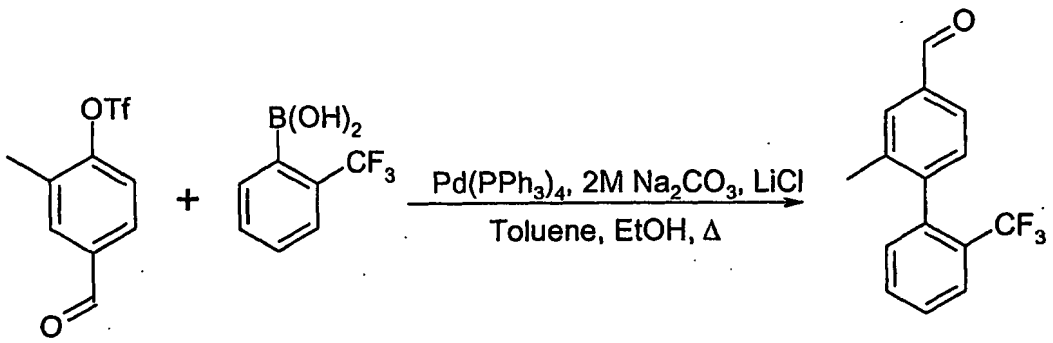


Compound 16a: 4-Formyl-2-methylphenyl trifluoromethanesulfonate



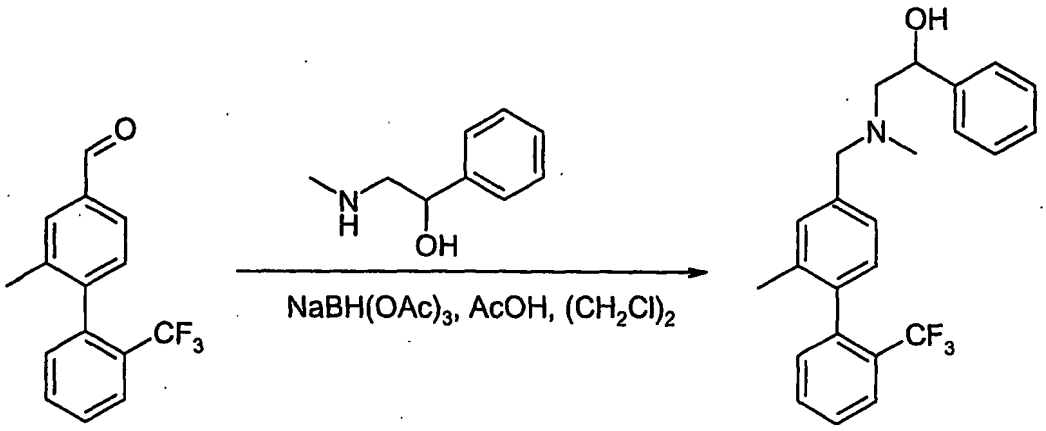
Following General Procedure 7, 4-hydroxy-3-methylbenzaldehyde (0.500 g, 3.67 mmol), DMAP (0.045 g, 0.37 mmol), NEt_3 (1.126 mL, 8.08 mmol), and triflic anhydride (1.139 g, 4.04 mmol) were combined. Silica gel column chromatography (8:2 Hexanes:EtOAc) provided the title compound (0.896 g, 91%) as a white solid. ^{1}H-NMR ($CDCl_3$): δ 10.01 (s, 1H), 7.86 (s, 1H), 7.81 (d, *J*=8.0 Hz, 1H), 7.44 (d, *J*=7.6 Hz, 1H), 2.48 (s, 3H).

Compound 16b: 2-Methyl-2'-(trifluoromethyl)-[1,1'-biphenyl]-4-carboxaldehyde



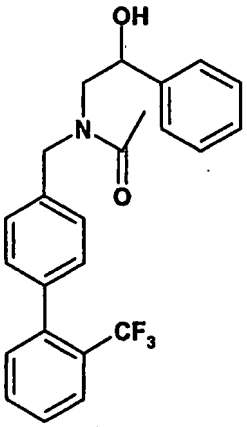
A solution of [2-(trifluoromethyl)phenyl]boronic acid (2.79 g, 14.66 mmol) in ethanol (35 mL) was added to a mixture of 4-formyl-2-methylphenyl trifluoromethanesulfonate (2.62 g, 9.78 mmol), LiCl (1.24 g, 29.33 mmol), $Pd(PPh_3)_4$ (0.57 g, 0.49 mmol), toluene (145 mL), and 2 M Na_2CO_3 (15 mL). The resulting mixture was heated at reflux for 24 h. The reaction was then concentrated *in vacuo*, and the residue was diluted with water (60 mL). The aqueous phase was extracted with EtOAc (3 x 60 mL). The combined organic phases were then washed with brine (80 mL), dried over Na_2SO_4, filtered, and concentrated *in vacuo* to provide the title compound (2.533 g, 95%). The crude material was of sufficient purity (>85%) to be used in subsequent steps. ^{1}H-NMR ($CDCl_3$): δ 10.04 (s, 1H), 7.80-7.78 (overlapping s at 7.78 and d at 7.79, *J*=7.6 Hz, 2H), 7.73 (d, *J*=7.6 Hz, 1H), 7.61 (t, *J*=7.6 Hz, 1H), 7.53 (t, *J*=7.6 Hz, 1H), 7.32 (d, *J*=8.0 Hz, 1H), 7.22 (d, *J*=7.6 Hz, 1H), 2.12 (s, 3H). MS (ESI) $(M+H)^+$ = 265.

Compound 16c: α-[[Methyl[[2-methyl-2'-(trifluoromethyl)[1,1'-biphenyl]-4-yl]methyl]amino]methyl]- benzenemethanol

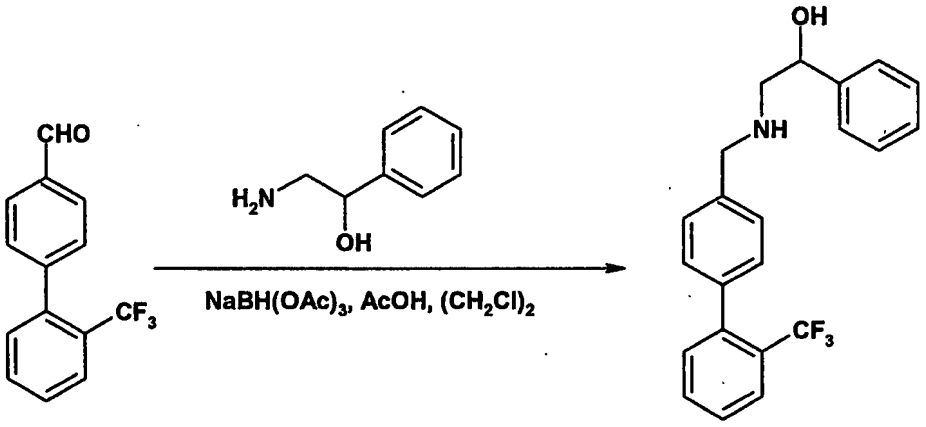


Following General Procedure 4, 2-methyl-2'-(trifluoromethyl)-[1,1'-biphenyl]-4-carboxaldehyde (1.076 g, 3.55 mmol), α-[(methylamino)methyl]benzenemethanol (0.200 g, 1.32 mmol), and $NaBH(OAc)_3$ (0.562 g, 2.65 mmol) were combined. The crude product was purified by reverse phase HPLC (gradient 30-85% CH_3CN in H_2O) to provide the title compound (0.267 g, 40%) as its TFA salt. This material was lyophilized from H_2O/acetonitrile to produce a white solid. Due to quaternization of the stereogenic nitrogen atom, a mixture of 2 diastereomeric salts was obtained. ^1H-NMR (CD_3OD): δ 7.80 (d, *J*=7.6 Hz, 1H), 7.66 (t, *J*=7.6 Hz, 1H), 7.57 (t, *J*=7.6 Hz, 1H), 7.47-7.22 (overlapping d at 7.26 and br m, *J*=7.6 Hz, 9H), 5.09 (dd, *J*=3.2 Hz, *J*=10.8 Hz, 1H), 4.69 (br d, *J*=12.4 Hz, 0.5H), 4.47-4.37 (br m, 1H), 4.25 (br d, *J*=13.2 Hz, 0.5H), 3.41-3.13 (br m, 2H), 3.05 (br s, 1.5H), 2.89 (br s, 1.5H), 2.07-2.05 (overlapping s at 2.07 and s at 2.05, 3H). MS (ESI) $(M+H)^+ = 400$. Anal. Calcd for $C_{24}H_{24}F_3NO + 0.1\ H_2O + 1.1$ TFA: C, 59.75; H, 4.84; N, 2.66. Found: C, 59.73; H, 4.81; N, 2.75.

Example 17: *N*-(2-Hydroxy-2-phenylethyl)-*N*-[[2'-(trifluoromethyl)[1,1'-biphenyl]-4-yl]methyl]acetamide

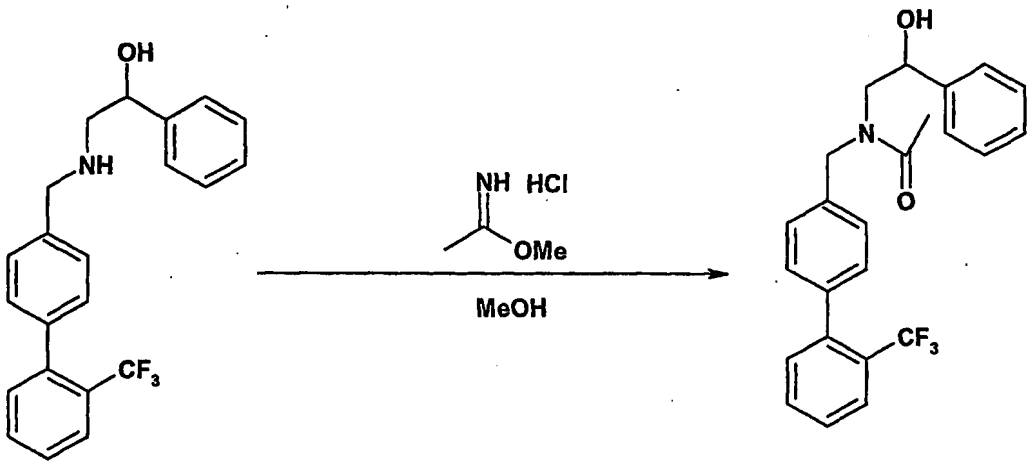


Compound 17a: α-[[[[2'-(Trifluoromethyl)[1,1'-biphenyl]-4-yl]methyl]amino]methyl]-benzenemethanol



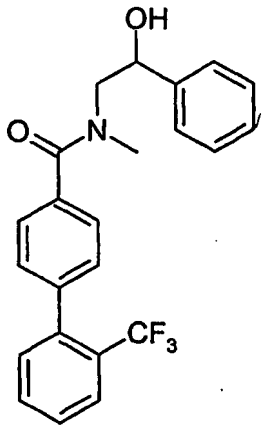
Following General Procedure 4, 2'-(trifluoromethyl)- [1,1'-biphenyl]-4-carboxaldehyde (0.121 g, 0.484 mmol), α-(aminomethyl)benzenemethanol (0.0975 g, 0.711 mmol), and $NaBH(OAc)_3$ (0.179 g, 0.846 mmol) were combined. The crude product was purified by flash chromatography (9:1 CH_2Cl_2:MeOH) to provide the title compound (0.133 g, 74%). ^{1}H-NMR ($CDCl_3$): δ 7.74 (d, *J*=8.0 Hz, 1H), 7.55 (t, *J*=7.2 Hz, 1H), 7.46 (t, *J*=8.0 Hz, 1H), 7.40-7.27 (m, 10H), 4.78 (dd, *J*=3.6 Hz, *J*=8.8 Hz, 1H), 3.89 (AB_q, *J*=13.2 Hz, 2H), 2.98 (dd, *J*=3.6 Hz, *J*=12.0 Hz, 1H), 2.81 (overlapping dd and br s, *J*=9.2 Hz, *J*=12.4 Hz for dd, 3H). MS (ESI) $(M+H)^+ = 372$.

Compound 17b: ***N*-(2-Hydroxy-2-phenylethyl)-*N*-[[2'-(trifluoromethyl)[1,1'-biphenyl]-4-yl]methyl]acetamide**

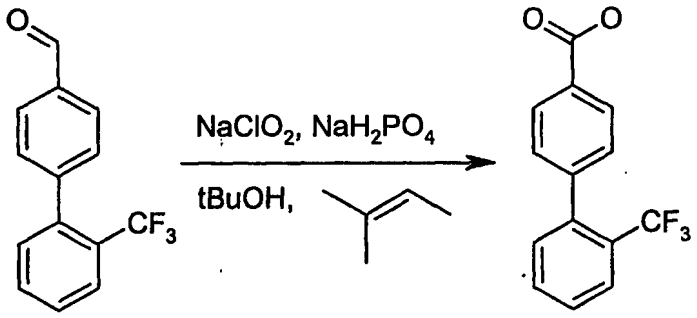


Methyl acetimidate hydrochloride (0.0847 g, 0.773 mmol) was added to a solution of α-[[[[2'-(trifluoromethyl)[1,1'-biphenyl]-4-yl]methyl]amino]methyl]benzenemethanol (0.0287 g, 0.0773 mmol) in dry MeOH (1 mL) maintained at 0 °C. The reaction was stirred for 6 d at room temperature, and then an additional portion of methyl acetimidate hydrochloride (0.0500 g, 0.456 mmol) was added. After stirring an additional 7 d, the reaction was concentrated *in vacuo*. The residue was dissolved in EtOAc (2 mL) and washed with a saturated solution of Na_2CO_3 (1 mL). The aqueous phase was back-extracted with additional EtOAc (3 x 1 mL). The combined organic phases were dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The residue was purified by reverse phase HPLC (gradient 20-60% CH_3CN in H_2O) to provide the title compound (0.0105 g, 33%). This material was lyophilized from H_2O/acetonitrile. Due to hindered rotation about the amide bond, rotamers were observed in the ^{1}H-NMR spectrum. ^{1}H-NMR (CD_3OD): δ 7.78-7.74 (m, 1H), 7.66-7.60 (m, 1H), 7.56-7.50 (m, 1H), 7.40-7.20 (m, 10H), 5.00 (dd, *J*=4.8 Hz, *J*=8.4 Hz, 0.4H), 4.93 (dd, *J*=4.8 Hz, *J*=8.0 Hz, 0.6H), 4.88 (d, *J*=14.8 Hz, 0.6H), 4.72 (d, *J*=17.2 Hz, 0.4H), 4.61-4.54 (m, 1H), 3.67-3.58 (m, 1H), 3.50 (dd, *J*=8.4 Hz, *J*=13.6 Hz, 0.4H), 3.39 (dd, *J*=4.8 Hz, *J*=15.2 Hz, 0.6H), 2.16 (s, 1.2H), 2.11 (s, 1.8H). MS (ESI) $(M+H)^+ = 414$. Anal. Calcd for $C_{24}H_{22}F_3NO_2$+0.3 TFA+0.6 H_2O: C, 64.45; H, 5.17; N, 3.06. Found: C, 64.55; H, 5.10; N, 3.50.

Example 18: *N*-(2-Hydroxy-2-phenylethyl)-*N*-methyl-2'-(trifluoromethyl)-[1,1'-biphenyl]-4-carboxamide

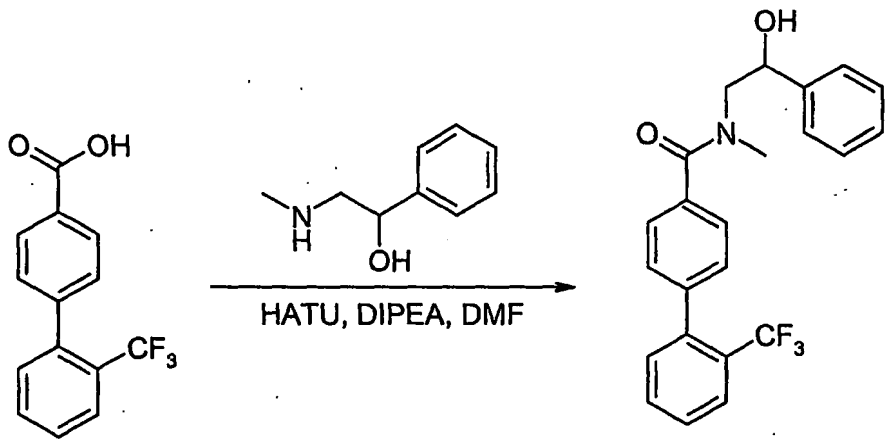


Compound 18a: 2'-(Trifluoromethyl)-[1,1'-biphenyl]-4-carboxylic acid



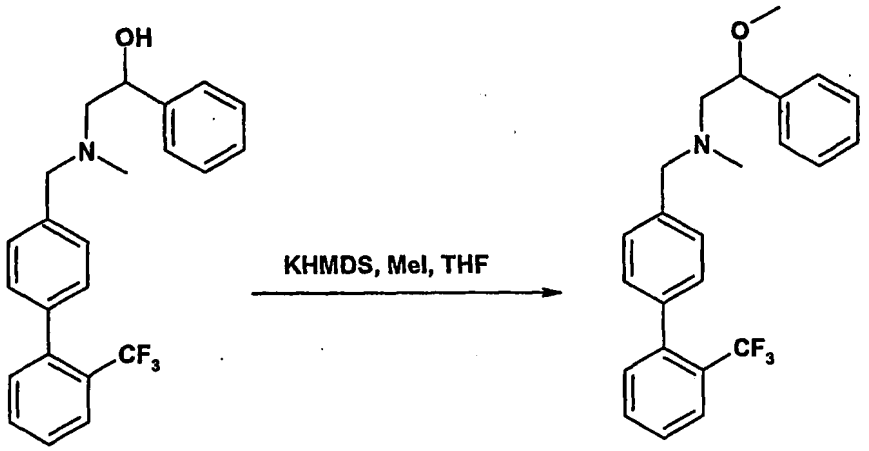
To a solution of 2'-(trifluoromethyl)- [1,1'-biphenyl]-4-carboxaldehyde (0.147 g, 0.59 mol) in t-BuOH (9 mL) and 2-methyl-2-butene (9 mL) was added a solution of $NaClO_2$ (0.496, 5.50 mmol) and NaH_2PO_4 (0.588 g, 4.9 mmol) in water (6 mL) in four portions over 0.5 h. The resulting reaction mixture was stirred for 5 h at room temperature, concentrated *in vacuo*, and the residue was diluted with water. The aqueous phase was extracted with CH_2Cl_2 (3 x). The product in the combined organic phases was then extracted into 1 N NaOH (3 x). The CH_2Cl_2 layer was discarded, the combined aqueous layers were acidified with 1 N HCl, and the product was back extracted with CH_2Cl_2 (3 x). The combined organic phases were then dried over Na_2SO_4, filtered, and concentrated *in vacuo* to provide the title compound (0.125 g, 80%) as a white solid. The crude material was of sufficient purity (>90%) to be used in subsequent steps. ^{1}H-NMR (CD_3OD): δ 8.06 (d, *J*=8.0 Hz, 2H), 7.79 (d, *J*=7.6 Hz, 1H), 7.66 (t, *J*=7.6 Hz, 1H), 7.57 (t, *J*=7.6 Hz, 1H), 7.42-7.36 (overlapping d at 7.41 and d at 7.37, *J*=8.0 Hz for both d, 3H).

Compound 18b: *N*-(2-Hydroxy-2-phenylethyl)-*N*-methyl-2'-(trifluoromethyl)-[1,1'-biphenyl]-4-carboxamide



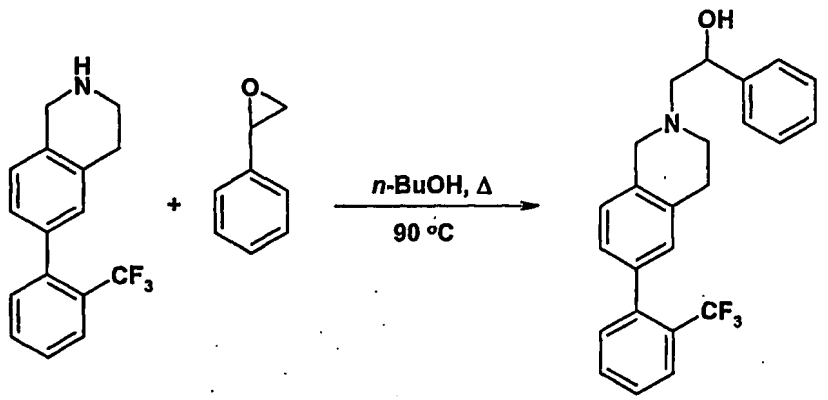
A solution of α-[(methylamino)methyl]benzenemethanol (0.013 g, 0.085 mmol) in DMF (0.5 mL) was added to a solution of 2'-(trifluoromethyl)-[1,1'-biphenyl]-4-carboxylic acid (0.025 g, 0.094 mmol), HATU (0.036 g, 0.094 mmol) and DIPEA (0.022 mL, 0.128 mmol) in DMF (0.5 mL). The reaction was carried out in a 48-well plate. The reaction was stirred overnight at room temperature, concentrated *in vacuo*, redissolved in EtOAc (1 mL), and washed with 1 N NaOH (3 x 1 mL) and water (2 x 1 mL). The organic phase was concentrated *in vacuo* to provide the title compound (0.027 g, 81%) with >90% purity. Due to hindered rotation about the amide bond, rotamers were observed in the ^{1}H-NMR spectrum. ^{1}H-NMR (CD_3OD): δ 7.77 (dd, *J*=2.0 Hz, *J*=7.6 Hz, 1H), 7.64 (t, *J*=7.4 Hz, 1H), 7.54 (t, *J*=7.6 Hz, 1H), 7.46 (d, *J*=7.6 Hz, 1H), 7.40-7.22 (d at 7.30, *J*=8.0 Hz, d at 7.23, *J*=8.0 Hz, br m, 8H), 7.10-7.08 (m, 1H), 5.08 (t, *J*=6.6 Hz, 0.5H), 4.81 (t, *J*=6.4 Hz, 0.5H), 3.74-3.72 (m, 1H), 3.50 (t, *J*=6.6 Hz, 1H), 3.21 (s, 1.5H), 2.94 (s, 1.5H). MS (ESI) $(M+H)^+ = 400$.

Example 19: β-Methoxy-*N*-methyl-*N*-[[2'-(trifluoromethyl)[1,1'-biphenyl]-4-yl]methyl]-benzeneethanamine



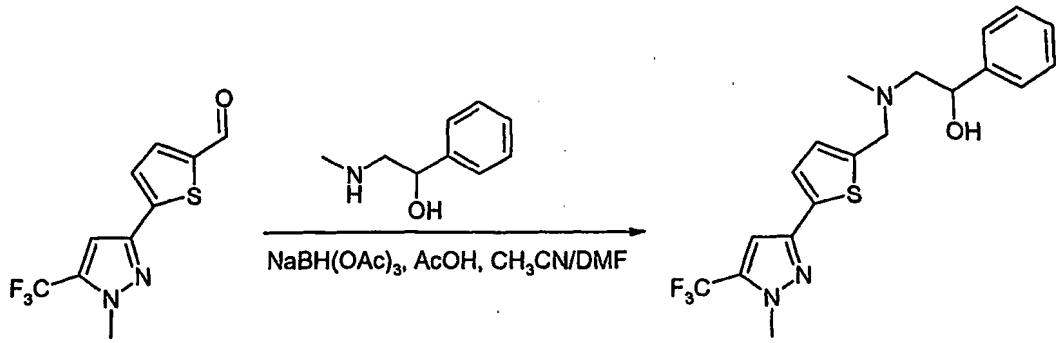
KHMDS (0.45 mL of 0.5M in toluene, 0.225 mmol) was added to a solution of α-[[methyl-[[2'-(trifluoromethyl)-[1,1'-biphenyl]-4-yl]methyl]amino]methyl]benzene-methanol (0.0286 g, 0.0742 mmol) in dry THF (3 mL). The mixture was stirred at room temperature for 20 min, and then neat iodomethane (4.6 μL, 0.074 mmol) was added. The reaction was stirred at room temperature for 19 h, and then quenched by the addition of H_2O (3 mL). The layers were separated, and the aqueous phase was extracted with CH_2Cl_2 (4 x 3 mL). The combined organic phases were then dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The residue was purified by reverse phase HPLC (gradient 20-70% CH_3CN in H_2O) to provide the title compound (0.0066 g, 17%) as its TFA salt. This material was lyophilized from H_2O/acetonitrile. Due to quaternization of the stereogenic nitrogen atom, a mixture of 2 diastereomeric salts was obtained. ^{1}H-NMR (CD_3OD): δ 7.82 (d, *J*=7.6 Hz, 1H), 7.72-7.56 (m, 4H), 7.54-7.30 (m, 8H), 4.78-4.65 (m, 1H), 4.62-4.42 (m, 1.5H), 4.36 (br d, *J*=12.4 Hz, 0.5H), 3.50-3.30 (m, 1.5H), 3.29 (s, 3H), 3.17 (br d, *J*=12.8 Hz, 0.5H), 3.06 (s, 1.5H), 2.94 (s, 1.5H). MS (ESI) $(M+H)^+ = 400$.

Example 20: 3,4-Dihydro-α-phenyl-6-[2-(trifluoromethyl)phenyl]-2(1*H*)-isoquinolineethanol



Following General Procedure 5, 1,2,3,4-tetrahydro-6-[2-(trifluoromethyl)phenyl]-isoquinoline (0.0247 g, 0.0891 mmol) and 2-(phenyl)oxirane (0.010 mL, 0.0877 mmol) were combined and heated at 90 °C for 16 h. The crude product was purified by reverse phase HPLC (gradient 25-45% CH_3CN in H_2O) to provide the title compound (0.0111 g, 24%) as its TFA salt. This material was lyophilized from H_2O/acetonitrile to produce a white, hygroscopic solid. Due to quaternization of the stereogenic nitrogen atom, a mixture of 2 diastereomeric salts was obtained. ^{1}H-NMR (CD_3OD): δ 7.79 (d, *J*=7.6 Hz, 1H), 7.67 (t, *J*=7.6 Hz, 1H), 7.57 (t, *J*=7.6 Hz, 1H), 7.55-7.48 (m, 2H), 7.45-7.39 (m, 2H), 7.38-7.24 (m, 5H), 5.27 (dd, *J*=3.2 Hz, *J*=10.0 Hz, 1H), 4.86-4.46 (br m, 2H), 4.12-3.90 (br m, 1H), 3.62-3.12 (br m, 5H). MS (ESI) $(M+H)^+$ = 398. Anal. Calcd for $C_{24}H_{22}F_3NO$+1.3 TFA+0.5 H_2O: C, 57.60; H, 4.42; N, 2.53. Found: C, 57.60; H, 4.35; N, 2.49.

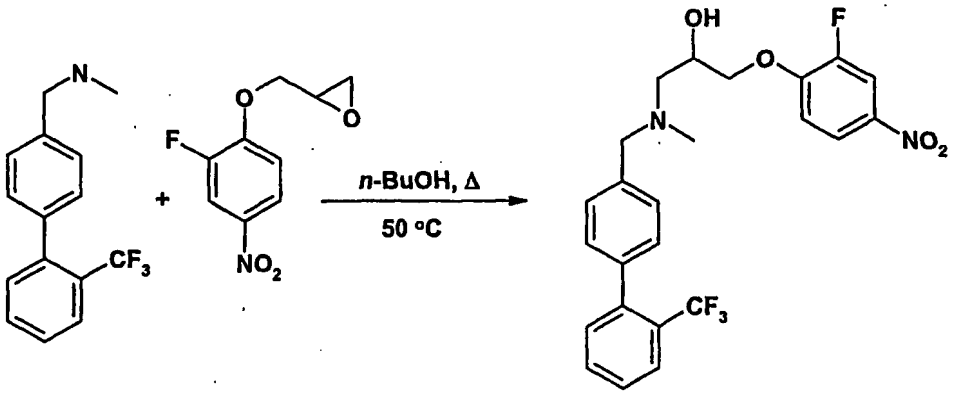
Example 21: α-[[Methyl[[5-[1-methyl-5-(trifluoromethyl)-1*H*-pyrazol-3-yl]-2-thienyl]methyl]amino]methyl]-benzenemethanol



A solution of 5-[1-methyl-5-(trifluoromethyl)-1*H*-pyrazol-3-yl]- 2-thiophenecarboxaldehyde (0.260 g, 0.77 mmol), α-

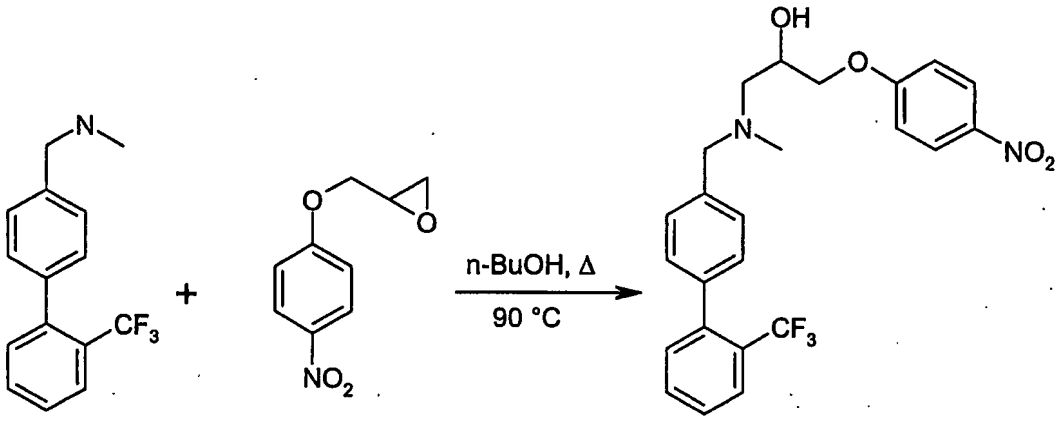
[(methylamino)methyl]benzenemethanol (0.151 g, 0.77 mmol), and acetic acid (0.080 mL) in CH_3CN (4 mL) was stirred for 3 days. A solution of $NaBH(OAc)_3$ (0.211 g, 3.87 mmol) in DMF (4 mL) was added and the reaction was stirred for 2 days, concentrated *in vacuo*, redissolved in CH_2Cl_2, and washed with 1 N NaOH. The layers were then filtered through a Hydromatrix® column and the product was eluted with CH_2Cl_2. The organic phase was concentrated *in vacuo* and purified by reverse phase HPLC (gradient 15-85% CH_3CN in H_2O) to provide the title compound (0.040 g, 10%) as its TFA salt. Due to quaternization of the stereogenic nitrogen atom, a mixture of 2 diastereomeric salts was obtained. ^{1}H-NMR (CD_3OD): δ 7.41-7.28 (br m, 7H), 6.81 (s, 1H), 5.10 (dd, *J*=6.0 Hz, *J*=7.6 Hz, 1H), 4.80-4.65 (br s at 4.75, s at 4.69, and s at 4.65, 2H), 4.01 (s, 3H), 3.33-3.27 (overlapping s at 3.33 and s at 3.30, 2H), 3.01 (br s, 3H). MS (ESI) $(M+H)^+ = 396$. Anal. Calcd for $C_{19}H_{20}F_3N_3OS + 0.2$ $H_2O + 1.0$ TFA: C, 54.02; H, 4.25; N, 4.85. Found: C, 54.05; H, 4.09; N, 4.85.

Example 22: 1-(2-Fluoro-4-nitrophenoxy)-3-[methyl[[2'-(trifluoromethyl)[1,1'-biphenyl]-4-yl]methyl]amino]-2-propanol



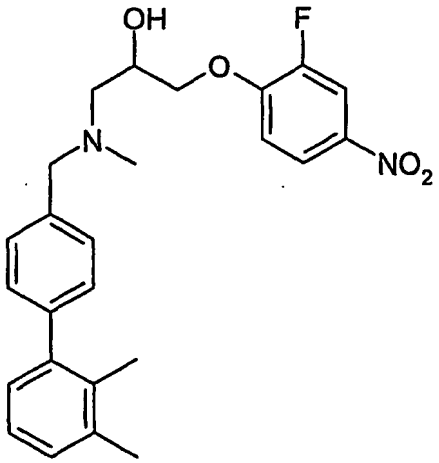
Following General Procedure 5, N-methyl-2'-(trifluoromethyl)- [1,1'-biphenyl]-4-methanamine (0.0800 g of 90% purity, 0.288 mmol) and 2-[(2-fluoro-4-nitrophenoxy)methyl]oxirane (0.0613 g, 0.288 mmol) were combined and heated at 50 °C for 24 h. The crude product was purified by reverse phase HPLC (gradient 20-60% CH_3CN in H_2O) to provide the title compound (0.030 g, 18%) as its TFA salt. This material was lyophilized from H_2O/acetonitrile. Due to quaternization of the stereogenic nitrogen atom, a mixture of 2 diastereomeric salts was obtained. ^{1}H-NMR (CD_3OD): δ 8.08 (d, *J*=9.2 Hz, 1H), 8.04 (dd, *J*=2.0 Hz, *J*=11.2 Hz, 1H), 7.79 (d, *J*=8.0 Hz, 1H), 7.66 (t, *J*=7.6 Hz, 1H), 7.60 (d, *J*=8.0 Hz, 2H), 7.57 (t, *J*=7.6 Hz, 1H), 7.44 (d, *J*=8.0 Hz, 2H), 7.36 (d, *J*=7.6 Hz, 1H), 7.30 (t, *J*=8.4 Hz, 1H), 4.72-4.16 (br m at 4.51, br s at 4.21, and underlying br m, 5H), 3.62-3.24 (br s at 3.55, br t at 3.40, br s at 3.28, *J*=11.2 Hz for t, 2H), 2.97 (br s, 3H). MS (ESI) $(M+H)^+ = 479$. Anal. Calcd for $C_{24}H_{22}F_4N_2O_4 + 0.1\ H_2O + 1.2$ TFA: C, 51.39; H, 3.82; N, 4.54. Found: C, 51.34; H, 3.73; N, 4.90.

Example 23: 1-[Methyl[[2'-(trifluoromethyl)[1,1'-biphenyl]-4-yl]methyl]amino]-3-(4-nitrophenoxy)-2-propanol

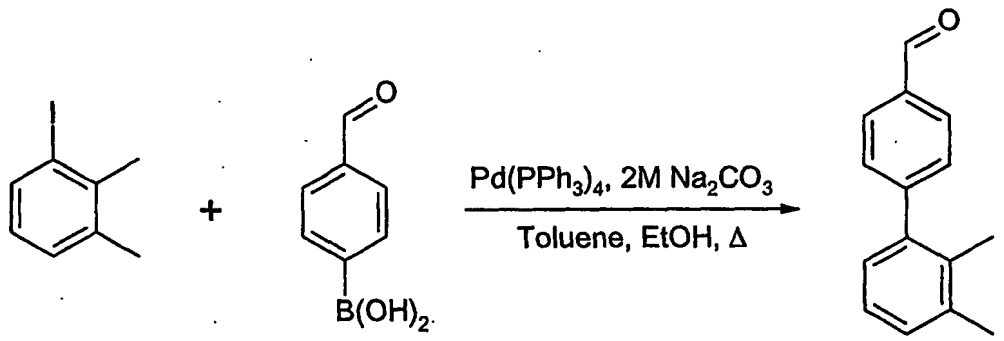


Following General Procedure 5, *N*-methyl-2'-(trifluoromethyl)-[1,1'-biphenyl]-4-methanamine (0.072 g, 0.29 mmol) and 2-[(4-nitrophenoxy)methyl]-oxirane (0.057 g, 0.29 mmol) were combined and heated at 50 °C for 24 h. The crude product was purified by reverse phase HPLC (gradient 20-60% CH_3CN in H_2O) to provide the title compound (0.034 g, 20%) as its TFA salt. This material was lyophilized from H_2O/ CH_3CN to produce a white solid. Due to quaternization of the stereogenic nitrogen atom, a mixture of 2 diastereomeric salts was obtained. ^{1}H-NMR (CD_3OD): δ 8.20 (d, *J*=9.2 Hz, 2H), 7.79 (d, *J*=7.6 Hz, 1H), 7.66 (t, *J*=7.6 Hz, 1H), 7.62-7.55 (overlapping d at 7.61 and t at 7.57, *J*=8.4 Hz for d and *J*=7.6 Hz for t, 3H), 7.44 (d, *J*=8.0 Hz, 2H), 7.35 (d, *J*=7.6 Hz, 1H), 7.09 (br d, *J*=8.4 Hz, 2H), 4.64-4.31 (overlapping br s at 4.64, br s at 4.31, and br m, 3H), 4.13 (br s, 2H), 3.53-3.29 (br s at 3.53, br t at 3.38, and br s at 3.29, *J*=11.6 Hz for t, 2H), 2.97 (br s, 3H). MS (ESI) $(M+H)^+$ = 461. Anal. Calcd for $C_{24}H_{23}F_3N_2O_4$ + 0.2 H_2O + 1.0 TFA: C, 54.02; H, 4.25; N, 4.85. Found: C, 54.05; H, 4.09; N, 4.85.

Example 24: 1-[[(2',3'-Dimethyl[1,1'-biphenyl]-4-yl)methyl]methylamino]-3-(2-fluoro-4-nitrophenoxy)-2-propanol

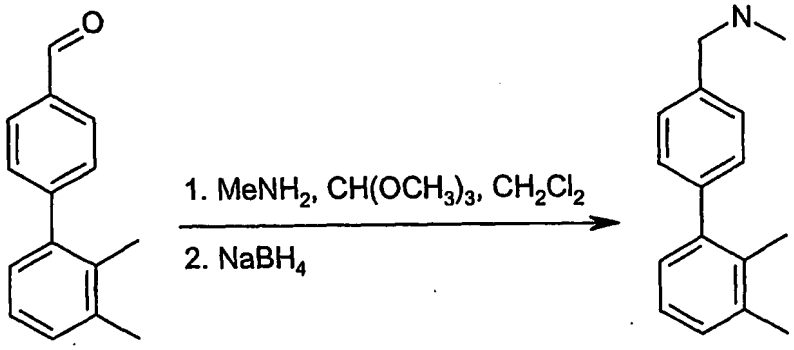


Compound 24a: 2',3'-Dimethyl-[1,1'-biphenyl]-4-carboxaldehyde



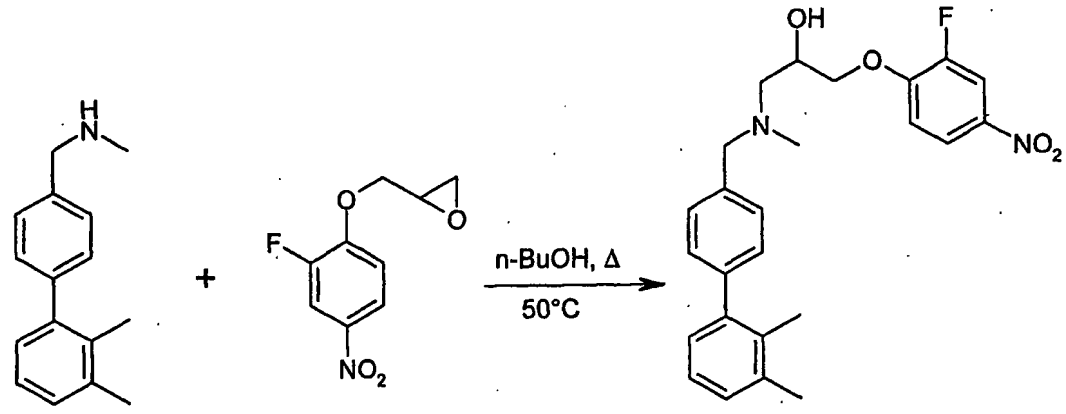
Following General Procedure 1, 1-iodo-2,3-dimethyl-benzene (2.06 g, 8.89 mmol), 4-formylphenylboronic acid (2.00 g, 13.34 mmol), $Pd(PPh_3)_4$ (0.51 g, 0.44 mmol), and 2 M Na_2CO_3 (31 mL, 62 mmol) were combined. Following the usual work-up provided the title compound (1.05 g, 56%). The crude material was of sufficient purity (>75%) to be used in the subsequent steps. ^{1}H-NMR ($CDCl_3$): δ 10.07 (s, 1H), 7.93 (d, *J*=7.6 Hz, 2H), 7.47 (d, *J*=8.0 Hz, 2H), 7.22-7.15 (m, 2H), 7.07 (d, *J*=6.4 Hz, 1H), 2.36 (s, 3H), 2.15 (s, 3H).

Compound 24b: ***N*,2',3'-Trimethyl-[1,1'-biphenyl]-4-methanamine**



2',3'-Dimethyl-[1,1'-biphenyl]-4-carboxaldehyde (0.351 g, 1.67 mmol) was treated according to General Procedure 3 to provide the title compound (0.120 g, 40%). The crude material was of sufficient purity (>80%) to be used in subsequent steps. ^{1}H-NMR ($CDCl_3$): δ 7.34 (d, *J*=8.0 Hz, 2H), 7.26 (d, *J*=8.0 Hz, 2H), 7.15-7.06 (m, 3H), 3.79 (br s, 2H), 2.49 (br s, 3H), 2.33 (s, 3H), 2.15 (s, 3H). MS (ESI) $(M+H)^+$ = 226.

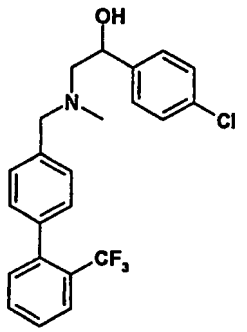
Compound 24c: 1-[[(2',3'-Dimethyl[1,1'-biphenyl]-4-yl)methyl]methylamino]-3-(2-fluoro-4-nitrophenoxy)-2-propanol



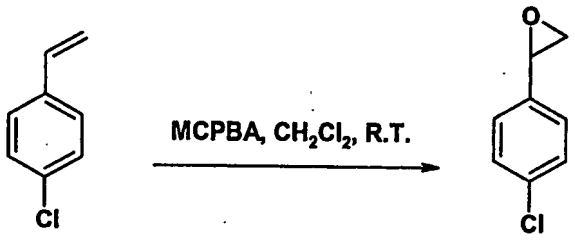
Following General Procedure 5, *N*,2',3'-trimethyl-[1,1'-biphenyl]-4-methanamine (0.063 g, 0.30 mmol) and 2-[(2-fluoro-4-nitrophenoxy)methyl]oxirane (0.64 g, 0.38 mmol) were combined and heated at 50 °C for 24 h. The crude product was purified by reverse phase HPLC (gradient 20-60% CH_3CN in H_2O) to provide the title compound (0.027 g, 16%) as its TFA salt. This material was lyophilized from H_2O/ CH_3CN to produce a white solid. Due to quaternization of the stereogenic nitrogen atom, a mixture of 2 diastereomeric salts was obtained. ^{1}H-NMR (CD_3OD): δ 8.09-8.02 (br m, 2H), 7.58 (d, *J*=8.0 Hz, 2H), 7.40 (d, *J*=8.0 Hz, 2H), 7.29 (br s, 1H), 7.15

(d, J=6.8 Hz, 1H), 7.10 (t, J=7.4 Hz, 1H), 6.98 (d, J=6.8 Hz, 1H), 4.62, (br s, 0.5H), 4.49 (br s, 2H), 4.27-4.26 (overlapping br s at 4.27 and br s at 4.26, 2.5H), 3.54-3.28 (br s at 3.54, br s at 3.39, and br s at 3.29, 2H), 3.00-2.95 (overlapping br s at 3.00 and br s at 2.95, 3H), 2.32 (s, 3H), 2.11 (s, 3H). MS (ESI) $(M+H)^+ = 439$. Anal. Calcd for $C_{25}H_{27}FN_2O_4 + 0.1\ H_2O + 1.6$ TFA: C, 54.39; H, 4.66; N, 4.50. Found: C, 54.30; H, 4.48; N, 4.41.

Example 25: 4-Chloro-α-[[methyl[[2'-(trifluoromethyl)[1,1'-biphenyl]-4-yl]methyl]amino]methyl]- benzenemethanol

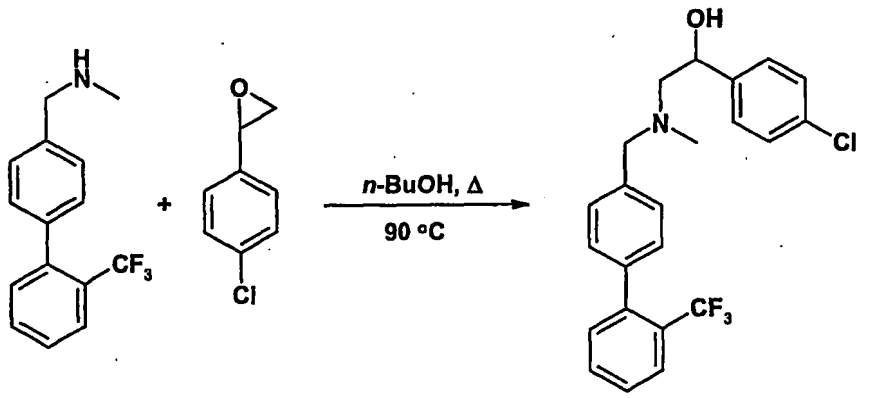


Compound 25a: 2-(4-Chlorophenyl)oxirane



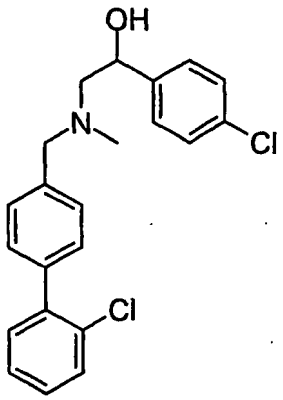
A solution of MCPBA (1.50 g of 60% purity, 5.22 mmol) in CH_2Cl_2 (10 mL) was added to a solution of 1-chloro-4-ethenylbenzene (0.554 g, 4.00 mmol) in CH_2Cl_2 (10 mL) maintained at 0 °C. The reaction was allowed to slowly warm to room temperature and stirred for 24 h. The mixture was filtered, and the filtrate was washed with saturated $NaHCO_3$. The organic phase was dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The residue was purified by column chromatography (9:1 Hexanes:EtOAc) to provide the title compound (0.198 g, 32%). ^{1}H-NMR ($CDCl_3$): δ 7.31 (d, J=8.8 Hz, 2H), 7.20 (d, J=8.8 Hz, 2H), 3.83 (distorted t, J=3.6 Hz, 1H), 3.14 (dd, J=4.0 Hz, J=5.6 Hz, 1H), 2.75 (dd, J=2.4 Hz, J=5.6 Hz, 1H).

Compound 25b: 4-Chloro-α-[[methyl[[2'-(trifluoromethyl)[1,1'-biphenyl]-4-yl]methyl]amino]methyl]- benzenemethanol

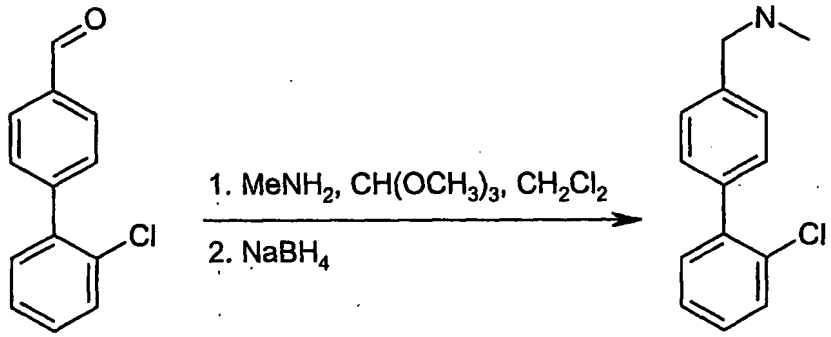


Following General Procedure 5, *N*-methyl-2'-(trifluoromethyl)- [1,1'-biphenyl]-4-methanamine (0.114 g of 90% purity, 0.387 mmol) and 2-(4-chlorophenyl)oxirane (0.060 g, 0.387 mmol) were combined and heated at 90 °C for 24 h. The crude product was purified by reverse phase HPLC (gradient 25-40% CH_3CN in H_2O) to provide the title compound (0.051 g, 24%) as its TFA salt. This material was lyophilized from H_2O/acetonitrile. Due to quaternization of the stereogenic nitrogen atom, a mixture of 2 diastereomeric salts was obtained. ^{1}H-NMR (CD_3OD): δ 7.78 (d, *J*=8.0 Hz, 1H), 7.65 (t, *J*=7.2 Hz, 1H), 7.62-7.52 (t and overlapping br m, *J*=7.6 Hz for t, 3H), 7.48-7.31 (m, 7H), 5.12-5.04 (m, 1H), 4.73 (br d, *J*=13.2 Hz, 0.5H), 4.45 (br m, 1H), 4.27 (br d, *J*=11.6 Hz, 0.5H), 3.46-3.12 (m, 2H), 3.03 (br s, 1.5H), 2.89 (br s, 1.5H). MS (ESI) $(M+H)^+$ = 420. Anal. Calcd for $C_{23}H_{21}ClF_3NO$+1.2 TFA+0.1 H_2O: C, 54.62; H, 4.04; N, 2.51. Found: C, 54.63; H, 3.83; N, 2.52.

Example 26: 4-Chloro-α-[[[(2'-chloro[1,1'-biphenyl]-4-yl)methyl]methylamino]methyl]-benzenemethanol

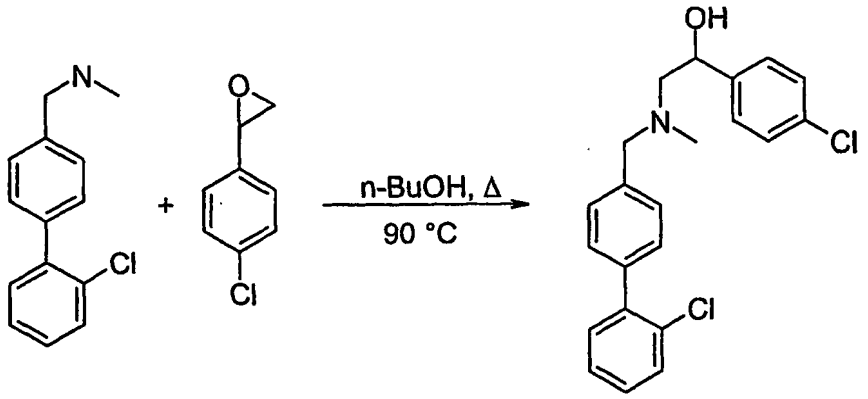


Compound 26a: 2'-Chloro-*N*-methyl-[1,1'-biphenyl]-4-methanamine



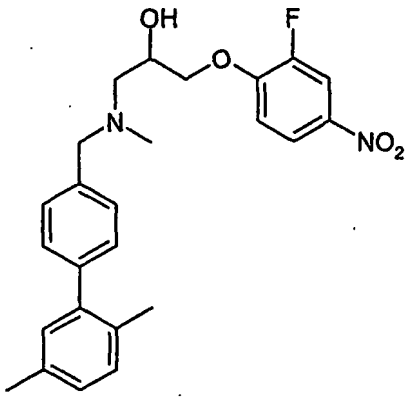
2'-Chloro-[1,1'-biphenyl]-4-carboxaldehyde (0.434 g, 2.00 mmol) was treated according to General Procedure 3 to provide the title compound (0.278 g, 75%). The crude material was of sufficient purity (>75%) to be used in subsequent steps. MS (ESI) $(M+H)^+ = 232$.

Compound 26b: 4-Chloro-α-[[[(2'-chloro[1,1'-biphenyl]-4-yl)methyl]methylamino]methyl]-benzenemethanol

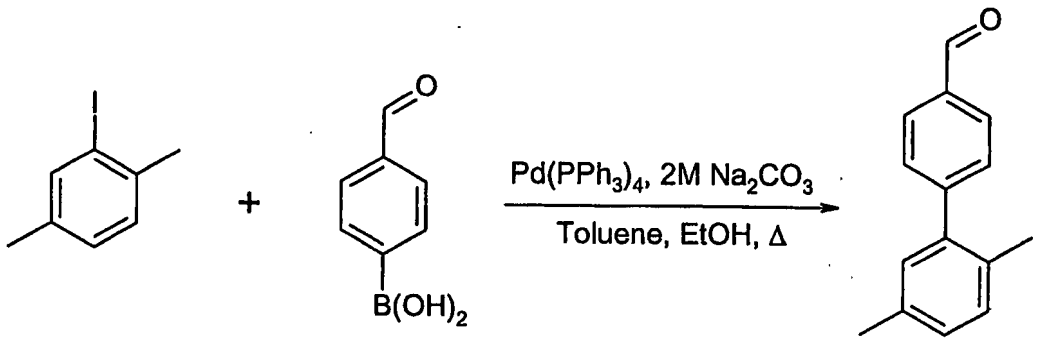


Following General Procedure 5, 2'-chloro-*N*-methyl-[1,1'-biphenyl]-4-methanamine (0.116 g, 0.50 mmol) and 2-(4-chlorophenyl)oxirane (0.078 g, 0.50 mmol) were combined and heated at 90 °C for 24 h. The crude product was purified by reverse phase HPLC (gradient 25-40% CH_3CN in H_2O) to provide the title compound (0.074 g, 30%) as its TFA salt. This material was lyophilized from H_2O/acetonitrile. Due to quaternization of the stereogenic nitrogen atom, a mixture of 2 diastereomeric salts was obtained. ^{1}H-NMR (CD_3OD): δ 7.63-7.50 (br m, 5H), 7.38 (br s, 7H), 5.11 (dd, *J*=3.4 Hz, *J*=10.6 Hz, 1H), 4.74 (br d, *J*=12.0 Hz, 0.5H), 4.47 (br s, 1H), 4.29 (br d, *J*=12.0 Hz, 0.5H), 3.41-3.17 (br d at 3.42, and br m, *J*=9.6 Hz for d, 2H), 3.05 (br s, 1.5H), 2.89 (br s, 1.5H). MS (ESI) $(M+H)^+$ = 386. Anal. Calcd for $C_{22}H_{21}Cl_2NO$ + 0.1 H_2O + 1.1 TFA: C, 56.60; H, 4.38; N, 2.73. Found: C, 56.49; H, 4.28; N, 2.70.

Example 27: 1-[[(2',5'-Dimethyl[1,1'-biphenyl]-4-yl)methyl]methylamino]-3-(2-fluoro-4-nitrophenoxy)-2-propanol

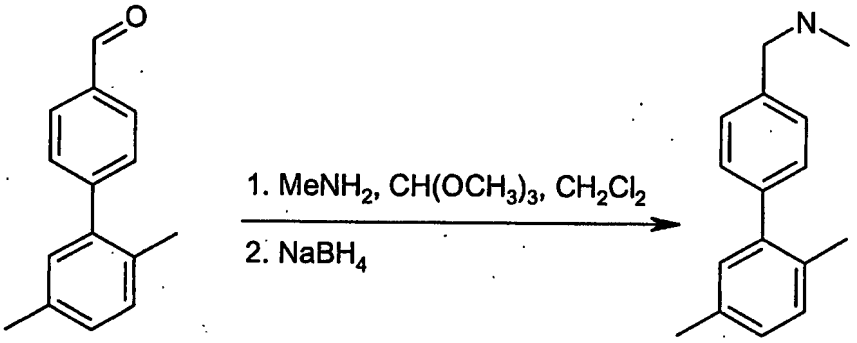


Compound 27a: 2',5'-Dimethyl-[1,1'-biphenyl]-4-carboxaldehyde



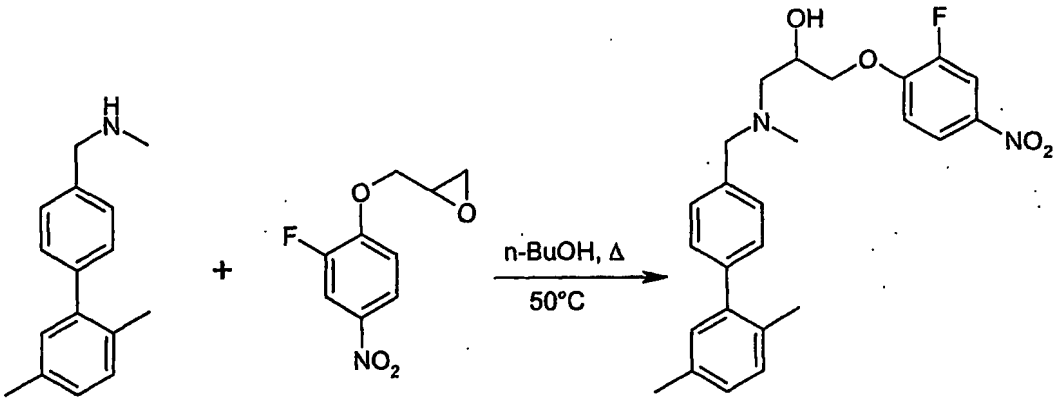
Following General Procedure 1, 2-iodo-1,4-dimethyl-benzene (2.06 g, 8.89 mmol), 4-formylphenylboronic acid (2.00 g, 13.34 mmol), $Pd(PPh_3)_4$ (0.51 g, 0.44 mmol), and 2 M Na_2CO_3 (31 mL, 62 mmol) were combined. Following the usual work-up provided the title compound (1.67 g, quantitative). The crude material was of sufficient purity (>90%) to be used in the subsequent steps. ^{1}H-NMR ($CDCl_3$): δ 10.06 (s, 1H), 7.92 (dd, *J*=1.8 Hz, *J*=8.2 Hz, 2H), 7.49 (dd, *J*=1.6 Hz, *J*=8.4 Hz, 2H), 7.18 (d, *J*=7.6 Hz, 1H), 7.12 (d, *J*=8.4 Hz, 1H), 7.05 (s, 1H), 2.36 (s, 3H), 2.23 (s, 3H).

Compound 27b: *N*,2',5'-Trimethyl-[1,1'-biphenyl]-4-methanamine



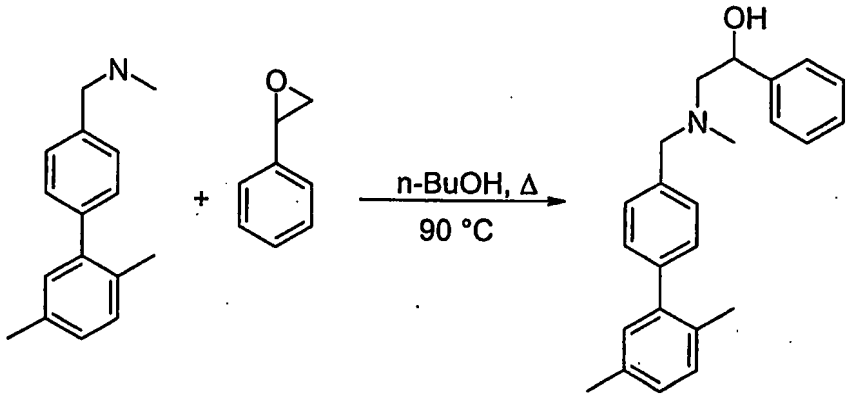
2',5'-Dimethyl-[1,1'-biphenyl]-4-carboxaldehyde (0.263 g, 1.25 mmol) was treated according to General Procedure 3 to provide the title compound (0.203 g, 80%). The crude material was of sufficient purity (>90%) to be used in subsequent steps. MS (ESI) $(M+H)^+ = 226$.

Compound 27c: 1-[[(2',5'-Dimethyl[1,1'-biphenyl]-4-yl)methyl]methylamino]-3-(2-fluoro-4-nitrophenoxy)-2-propanol



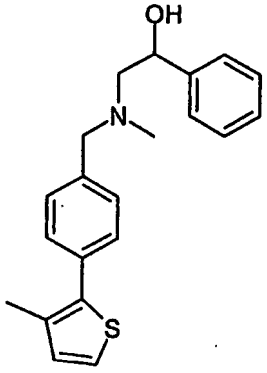
Following General Procedure 5, *N*,2',5'-trimethyl-[1,1'-biphenyl]-4-methanamine (0.068 g, 0.30 mmol) and 2-[(2-fluoro-4-nitrophenoxy)methyl]oxirane (0.64 g, 0.38 mmol) were combined and heated at 50 °C for 24 h. The crude product was purified by reverse phase HPLC (gradient 25-40% CH_3CN in H_2O) to provide the title compound (0.056 g, 34%) as its TFA salt. This material was lyophilized from H_2O/ CH_3CN to produce a white solid. Due to quaternization of the stereogenic nitrogen atom, a mixture of 2 diastereomeric salts was obtained. ^{1}H-NMR (CD_3OD): δ 8.08-8.00 (br m, 2H), 7.56 (d, *J*=8.4 Hz, 2H), 7.40 (d, *J*=8.4 Hz, 2H), 7.27 (br s, 1H), 7.13 (d, *J*=7.6 Hz, 1H), 7.05 (d, *J*=8.0 Hz, 1H), 6.96 (s, 1H), 4.61, (br s, 0.5H), 4.46 (br s, 2H), 4.28-4.18 (overlapping br d at 4.26 and br s at 4.18, *J*=15.2 Hz, 2.5H), 3.54-3.22 (br d at 3.52, br s at 3.39, and br s at 3.22, *J*=12.4 Hz, 2H), 2.98-2.91 (overlapping br s at 2.98 and br s at 2.91, 3H), 2.29 (s, 3H), 2.15 (s, 3H). MS (ESI) $(M+H)^+ = 439$. Anal. Calcd for $C_{25}H_{27}FN_2O_4 + 0.4\ H_2O + 1.2$ TFA: C, 56.49; H, 5.02; N, 4.81. Found: C, 56.46; H, 5.01; N, 4.86.

Example 28: α-[[[(2',5'-Dimethyl[1,1'-biphenyl]-4-yl)methyl]methylamino]methyl]-benzenemethanol

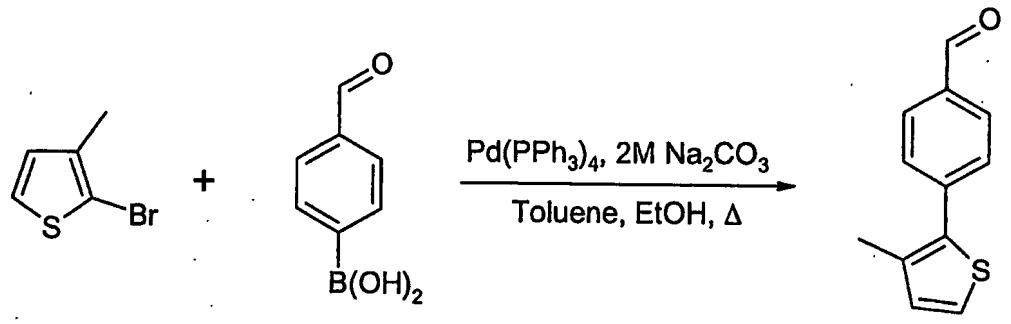


Following General Procedure 5, *N*,2',5'-trimethyl-[1,1'-biphenyl]-4-methanamine (0.072 g, 0.32 mmol) and 2-phenyl-oxirane (0.038 g, 0.32 mmol) were combined and heated at 90 °C for 24 h. The crude product was purified by reverse phase HPLC (gradient 25-40% CH_3CN in H_2O) to provide the title compound (0.033 g, 22%) as its TFA salt. This material was lyophilized from H_2O/acetonitrile. Due to quaternization of the stereogenic nitrogen atom, a mixture of 2 diastereomeric salts was obtained. ^{1}H-NMR (CD_3OD): δ 7.54 (br s, 2H), 7.40-7.31 (br m, 7H), 7.13 (d, *J*=8.0 Hz, 1H), 7.05 (d, *J*=7.6 Hz, 1H), 6.98 (s, 1H), 5.08 (dd, *J*=3.6 Hz, *J*=10.8 Hz, 1H), 4.71 (br d, *J*=10.0 Hz, 0.5H), 4.44 (br s, 1H), 4.27 (br d, *J*=13.2 Hz, 0.5H), 3.41-3.16 (br d at 3.39, and br m, *J*=12.8 Hz for d, 2H), 3.03 (br s, 1.5H), 2.87 (br s, 1.5H), 2.29 (s, 3H), 2.16 (s, 3H). MS (ESI) $(M+H)^+$ = 346. Anal. Calcd for $C_{24}H_{27}NO$ + 0.6 H_2O + 1.0 TFA: C, 66.40; H, 6.26; N, 2.98. Found: C, 66.45; H, 6.16; N, 2.68.

Example 29: α-[[Methyl[[4-(3-methyl-2-thienyl)phenyl]methyl]amino]methyl]-benzenemethanol

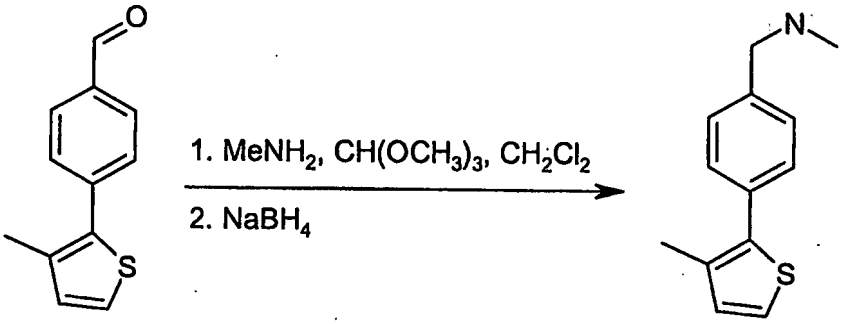


Compound 29a: 4-(3-Methyl-2-thienyl)-benzaldehyde



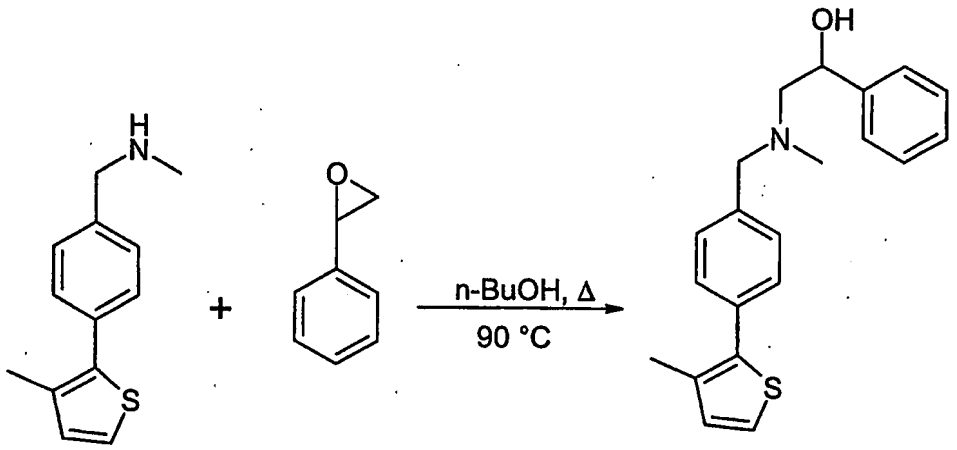
Following General Procedure 1, 2-bromo-3-methyl-thiophene (0.88 g, 4.95 mmol), 4-formylphenylboronic acid (1.11 g, 7.43 mmol), $Pd(PPh_3)_4$ (0.29 g, 0.25 mmol), and 2 M Na_2CO_3 (15 mL, 35 mmol) were combined. Following the usual work-up provided the title compound (0.579 g, 58%). The crude material was of sufficient purity (>50%) to be used in subsequent steps. ^{1}H-NMR ($CDCl_3$): δ 10.04 (s, 1H), 7.92 (d, *J*=8.4 Hz, 2H), 7.64 (d, *J*=8.4 Hz, 2H), 7.30 (d, *J*=5.2 Hz, 1H), 6.97 (d, *J*=5.2 Hz, 1H), 2.39 (s, 3H).

Compound 29b: ***N*-Methyl-4-(3-methyl-2-thienyl)-benzenemethanamine**



4-(3-Methyl-2-thienyl)-benzaldehyde (0.253 g, 1.25 mmol) was treated according to General Procedure 3 to provide the title compound (0.139 g, 57%). The crude material was of sufficient purity (>90%) to be used in subsequent steps. ^{1}H-NMR ($CDCl_3$): δ 7.55 (d, *J*=8.4 Hz, 1H), 7.42 (d, *J*=8.4 Hz, 1H), 7.38-7.33 (overlapping d at 7.37, *J*=8.4 Hz, and d at 7.34, *J*=8.4 Hz, 2H), 7.18 (d, *J*=5.2 Hz, 1H), 6.91 (d, *J*=5.2 Hz, 1H), 3.77 (s, 2H), 2.47 (s, 3H), 2.32 (s, 3H). MS (ESI) $(M+H)^+ = 218$.

Compound 29c: α-[[Methyl[[4-(3-methyl-2-thienyl)phenyl]methyl]amino]methyl]-benzenemethanol



Following General Procedure 5, *N*-methyl-4-(3-methyl-2-thienyl)-benzenemethanamine (0.109 g, 0.50 mmol) and 2-phenyl-oxirane (0.060 g, 0.50 mmol) were combined and heated at 90 °C for 24 h. The crude product was purified by reverse phase HPLC (gradient 20-30% CH_3CN in H_2O) to provide the title compound (0.032 g, 14%) as its TFA salt. This material was lyophilized from H_2O/acetonitrile. Due to quaternization of the stereogenic nitrogen atom, a mixture of 2 diastereomeric salts was obtained. ^{1}H-NMR (CD_3OD): δ 7.62-7.57 (m, 4H), 7.42-7.33 (overlapping d at 7.33 and m, *J*=4.8 Hz for d, 6H), 6.96 (d, *J*=5.2 Hz, 1H), 5.12 (br s, 1H), 4.73 (br d, *J*=12.8 Hz, 0.5H), 4.45 (br s, 1H), 4.27 (br d, *J*=13.2 Hz, 0.5H), 3.43-3.18 (br d at 3.42, *J*=12.4 Hz, br d at 3.18, *J*=11.2 Hz, and br m, 2H), 3.04 (s, 1.5H), 2.88 (s, 1.5H), 2.33 (s, 3H). MS (ESI) $(M+H)^+$ = 338. Anal. Calcd for $C_{21}H_{23}NOS$ + 0.8 H_2O + 1.1 TFA: C, 58.38; H, 5.43; N, 2.93. Found: C, 58.48; H, 5.41; N, 2.93.

EXAMPLES 30- 132

Additional exemplary compounds were prepared according to the general procedures and the examples described above. Mass spectra of these compounds were obtained to confirm the formation of these compounds. These exemplary compounds and the mass spectrum results thereof are listed in Table 2 below.

Table 2

Example No.	Compound Name	MS (ESI) $(M+H)^+$
30	1-[4-(1,1-Dimethylethyl)phenoxy]-3-[methyl[[2'-(trifluoromethyl)[1,1'-biphenyl]-4-yl]methyl]amino]-2-propanol	472
31	1-[4-(1,1-Dimethylethyl)phenoxy]-3-[[(2'-methoxy[1,1'-biphenyl]-4-yl)methyl]methylamino]-2-propanol	434
32	β-Ethoxy-*N*-methyl-*N*-[[2'-(trifluoromethyl)[1,1'-biphenyl]-4-yl]methyl]benzeneethanamine	414
33	*N*-Methyl-*N*-[[2'-(trifluoromethyl)[1,1'-biphenyl]-4-yl]methyl]glycylglycine, ethyl ester	409
34	*N*-Ethyl-2-[methyl[[2'-(trifluoromethyl)[1,1'-biphenyl]-4-yl]methyl]amino]acetamide	351
35	α-[(2-Fluoro-4-nitrophenoxy)methyl]-3,4-dihydro-7-[2-(trifluoromethyl)phenyl]-2(1*H*)-isoquinolineethanol	491
36	α-[[Methyl[(2,2',5'-trimethyl[1,1'-biphenyl]-4-yl)methyl]amino]methyl]benzenemethanol	360
37	1-[[[2'-Chloro-5'-(trifluoromethyl)[1,1'-biphenyl]-4-yl]methyl]methylamino]-3-(2-fluoro-4-nitrophenoxy)-2-propanol	513
38	4'-[[[3-(2-Fluoro-4-nitrophenoxy)-2-hydroxypropyl]methylamino]methyl]-6-methoxy-[1,1'-biphenyl]-3-carbonitrile	466
39	1-[[(2',5'-Dichloro[1,1'-biphenyl]-4-yl)methyl]methylamino]-3-(2-fluoro-4-nitrophenoxy)-2-propanol	479
40	1-[[[4-(2-Chloro-3-thienyl)phenyl]methyl]methylamino]-3-(2-fluoro-4-nitrophenoxy)-2-propanol	451
41	4'-[[[3-(2-Fluoro-4-nitrophenoxy)-2-hydroxypropyl]methylamino]methyl]-[1,1'-biphenyl]-2-carbonitrile	436
42	1-[[(2'-Chloro-5'-methyl[1,1'-biphenyl]-4-yl)methyl]methylamino]-3-(2-fluoro-4-nitrophenoxy)-2-propanol	459
43	1-[[(5'-Chloro-2'-methyl[1,1'-biphenyl]-4-yl)methyl]methylamino]-3-(2-fluoro-4-nitrophenoxy)-2-propanol	459
44	1-(2-Fluoro-4-nitrophenoxy)-3-[methyl[(2'-nitro[1,1'-biphenyl]-4-yl)methyl]amino]-2-propanol	456

Example No.	Compound Name	MS (ESI) $(M+H)^+$
45	α-[[[[4-(2-Chloro-3-thienyl)phenyl]methyl]methylamino]methyl]benzenemethanol	358/360
46	4'-[[(2-Hydroxy-2-phenylethyl)methylamino]methyl]- [1,1'-biphenyl]-2-carbonitrile	343
47	α-[[[(5'-Chloro-2'-methyl[1,1'-biphenyl]-4-yl)methyl]methylamino]methyl]benzenemethanol	366/368
48	α-[[Methyl[[2'-methyl-5'-(trifluoromethyl)[1,1'-biphenyl]-4-yl]methyl]amino]methyl]benzenemethanol	400
49	α-[[[[2'-Chloro-5'-(trifluoromethyl)[1,1'-biphenyl]-4-yl]methyl]methylamino]methyl]benzenemethanol	420/422
50	4'-[[(2-Hydroxy-2-phenylethyl)methylamino]methyl]-6-methoxy-[1,1'-biphenyl]-3-carbonitrile	373
51	α-[[[(2'-Fluoro[1,1'-biphenyl]-4-yl)methyl]methylamino]methyl]benzenemethanol	336
52	α-[[[(2',5'-Dichloro[1,1'-biphenyl]-4-yl)methyl]methylamino]methyl]-benzenemethanol	386/388/390
53	Methyl 3-[4-[[(2-hydroxy-2-phenylethyl)methylamino]methyl]phenyl]-2-thiophenecarboxylate	382
54	α-[[Methyl[[2'-(1-methylethoxy)[1,1'-biphenyl]-4-yl]methyl]amino]methyl]benzenemethanol	376
55	α-[[[(2'-Ethoxy[1,1'-biphenyl]-4-yl)methyl]methylamino]methyl]benzenemethanol	362
56	α-[[Methyl[[2'-(2-propenyl)[1,1'-biphenyl]-4-yl]methyl]amino]methyl]benzenemethanol	358
57	α-[[[(2'-Cyclopentyl[1,1'-biphenyl]-4-yl)methyl]methylamino]methyl]benzenemethanol	386
58	α-[[Methyl[[5'-methyl-2'-(1-methylethyl)[1,1'-biphenyl]-4-yl]methyl]amino]methyl]benzenemethanol	374
59	α-[[[(2'-Methoxy-5'-methyl[1,1'-biphenyl]-4-yl)methyl]methylamino]methyl]-benzenemethanol	362
60	1-(2-Fluoro-4-nitrophenoxy)-3-[methyl[[2'-methyl-5'-(trifluoromethyl)[1,1'-biphenyl]-4-yl]methyl]amino]-2-propanol	493

Example No.	Compound Name	MS (ESI) $(M+H)^+$
61	α-[[[[5-(4-Bromophenyl)-2-furanyl]methyl]methylamino]methyl]benzenemethanol	386/388
62	α-[[[[5-(4-Chlorophenyl)-2-furanyl]methyl]methylamino]methyl]benzenemethanol	342
63	α-[[Methyl[[5-[3-(trifluoromethyl)phenyl]-2-furanyl]methyl]amino]methyl]benzenemethanol	376
64	Methyl 3-[5-[[(2-hydroxy-2-phenylethyl)methylamino]methyl]-2-furanyl]-2-thiophenecarboxylate	372
65	α-[[Methyl[[4-(3-pyridinyl)phenyl]methyl]amino]methyl]benzenemethanol	319
66	1-[[(2'-Chloro[1,1'-biphenyl]-4-yl)methyl]methylamino]-3-[4-(1,1-dimethylethyl)phenoxy]-2-propanol	438
67	1-(4-Chlorophenoxy)-3-[methyl[[2'-(trifluoromethyl)[1,1'-biphenyl]-4-yl]methyl]amino]-2-propanol	450
68	1-[Methyl[[2'-(trifluoromethyl)[1,1'-biphenyl]-4-yl]methyl]amino]-3-phenoxy-2-propanol	416
69	1-[[(2'-Methoxy[1,1'-biphenyl]-4-yl)methyl]methylamino]-3-(4-nitrophenoxy)-2-propanol	423
70	α-[[Methyl[[2'-(trifluoromethyl)[1,1'-biphenyl]-4-yl]methyl]amino]methyl]benzeneethanol	400
71	1-(1,1-Dimethylethoxy)-3-[methyl[[2'-(trifluoromethyl)[1,1'-biphenyl]-4-yl]methyl]amino]-2-propanol	396
72	Methyl 2-hydroxy-2-methyl-3-[methyl[[2'-(trifluoromethyl)[1,1'-biphenyl]-4-yl]methyl]amino]propanoate	382
73	(β^1S)-β-[[(2'-Chloro[1,1'-biphenyl]-4-yl)methyl]methylamino]-cyclohexanepropanol	372
74	1-(4-Chlorophenoxy)-3-[[(2'-methyl[1,1'-biphenyl]-4-yl)methyl]-2-propenylamino]-2-propanol	422
75	1-[[(2'-Methyl[1,1'-biphenyl]-4-yl)methyl]-2-propenylamino]-3-phenoxy-2-propanol	388
76	1-[[(2'-Chloro[1,1'-biphenyl]-4-yl)methyl]-2-propenylamino]-3-phenoxy-2-propanol	408

Example No.	Compound Name	MS (ESI) $(M+H)^+$
77	1-Phenoxy-3-[2-propenyl[[2'-(trifluoromethyl)[1,1'-biphenyl]-4-yl]methyl]amino]-2-propanol	442
78	1-[[(2'-Chloro[1,1'-biphenyl]-4-yl)methyl]-2-propenylamino]-3-(3,4-dichlorophenoxy)-2-propanol	476
79	1-[([1,1'-Biphenyl]-4-ylmethyl)-2-propenylamino]-3-(4-nitrophenoxy)-2-propanol	419
80	1-[[(2'-Methyl[1,1'-biphenyl]-4-yl)methyl]-2-propenylamino]-3-(4-nitrophenoxy)-2-propanol	433
81	1-[[(2'-Chloro[1,1'-biphenyl]-4-yl)methyl]-2-propenylamino]-3-(4-nitrophenoxy)-2-propanol	453
82	1-(4-Nitrophenoxy)-3-[2-propenyl[[2'-(trifluoromethyl)[1,1'-biphenyl]-4-yl]methyl]amino]-2-propanol	487
83	(α^1S)-α-[[[(2'-Methyl[1,1'-biphenyl]-4-yl)methyl]-2-propenylamino]methyl]benzenemethanol	358
84	(α^1S)-α-[[[(2'-Chloro[1,1'-biphenyl]-4-yl)methyl]-2-propenylamino]methyl]benzenemethanol	378
85	(2*R*)-3-[[(2'-Chloro[1,1'-biphenyl]-4-yl)methyl]-2-propenylamino]-2-hydroxypropyl butanoate	402
86	(2*R*)-2-Hydroxy-3-[2-propenyl[[2'-(trifluoromethyl)[1,1'-biphenyl]-4-yl]methyl]amino]propyl butanoate	436
87	Methyl 2-hydroxy-2-methyl-3-[2-propenyl[[2'-(trifluoromethyl)[1,1'-biphenyl]-4-yl]methyl]amino]propanoate	408
88	1-(3-Fluoro-4-nitrophenoxy)-3-[methyl[[2'-(trifluoromethyl)[1,1'-biphenyl]-4-yl]methyl]amino]-2-propanol	479
89	1-(4-Iodophenoxy)-3-[methyl[[2'-(trifluoromethyl)[1,1'-biphenyl]-4-yl]methyl]amino]-2-propanol	542
90	1-(3-Fluorophenoxy)-3-[methyl[[2'-(trifluoromethyl)[1,1'-biphenyl]-4-yl]methyl]amino]-2-propanol	434
91	Ethyl 4-[2-hydroxy-3-[methyl[[2'-(trifluoromethyl)[1,1'-biphenyl]-4-yl]methyl]amino]propoxy]-benzenecarboximidate	487
92	1-[[(2'-Chloro[1,1'-biphenyl]-4-yl)methyl]methylamino]-3-(3-fluoro-4-nitrophenoxy)-2-propanol	445

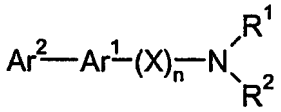
Example No.	Compound Name	MS (ESI) $(M+H)^+$
93	1-[[(2'-Chloro[1,1'-biphenyl]-4-yl)methyl]methylamino]-3-(2-fluoro-4-nitrophenoxy)-2-propanol	445
94	1-[[(2'-Chloro[1,1'-biphenyl]-4-yl)methyl]methylamino]-3-(4-nitrophenoxy)-2-propanol	427
95	1-[[(2',3'-Dimethyl[1,1'-biphenyl]-4-yl)methyl]methylamino]-3-phenoxy-2-propanol	376
96	1-[[(2',3'-Dimethyl[1,1'-biphenyl]-4-yl)methyl]methylamino]-3-(4-nitrophenoxy)-2-propanol	421
97	*N,N*-Diethyl-4-[3-[[(5'-fluoro-2'-methyl[1,1'-biphenyl]-4-yl)methyl]methylamino]-2-hydroxypropoxy]-3-methoxybenzamide	509
98	Ethyl 4-[3-[[(5'-fluoro-2'-methyl[1,1'-biphenyl]-4-yl)methyl]methylamino]-2-hydroxypropoxy]benzenecarboximidate	451
99	4-[3-[[[4'-Chloro-2'-(trifluoromethyl)[1,1'-biphenyl]-4-yl]methyl]methylamino]-2-hydroxypropoxy]-*N,N*-diethyl-3-methoxybenzamide	579
100	2-[3-[[[4'-Chloro-2'-(trifluoromethyl)[1,1'-biphenyl]-4-yl]methyl]methylamino]-2-hydroxypropoxy]benzamide	493
101	1-[[[4'-Chloro-2'-(trifluoromethyl)[1,1'-biphenyl]-4-yl]methyl]methylamino]-3-(3-methoxyphenoxy)-2-propanol	480
102	1-[[[4'-Chloro-2'-(trifluoromethyl)[1,1'-biphenyl]-4-yl]methyl]methylamino]-3-(1*H*-indol-5-yloxy)-2-propanol	489
103	Ethyl 4-[3-[[[4'-chloro-2'-(trifluoromethyl)[1,1'-biphenyl]-4-yl]methyl]methylamino]-2-hydroxypropoxy]benzenecarboximidate	521
104	1-[[[4'-Chloro-2'-(trifluoromethyl)[1,1'-biphenyl]-4-yl]methyl]methylamino]-3-phenoxy-2-propanol	450
105	1-[[[4'-Chloro-2'-(trifluoromethyl)[1,1'-biphenyl]-4-yl]methyl]methylamino]-3-(4-nitrophenoxy)-2-propanol	495
106	2-Fluoro-α-[[methyl[[2'-(trifluoromethyl)[1,1'-biphenyl]-4-yl]methyl]amino]methyl]benzenemethanol	404

Example No.	Compound Name	MS (ESI) $(M+H)^+$
107	α-[[[(2'-Chloro[1,1'-biphenyl]-4-yl)methyl]methylamino]methyl]-2-fluorobenzenemethanol	370
108	α-[[[(2'-Chloro-6'-methyl[1,1'-biphenyl]-4-yl)methyl]methylamino]methyl]benzenemethanol	366
109	α-[[[(2',5'-Dimethyl[1,1'-biphenyl]-4-yl)methyl]methylamino]methyl]-2-fluorobenzenemethanol	364
110	4-Chloro-α-[[[(2',5'-dimethyl[1,1'-biphenyl]-4-yl)methyl]methylamino]methyl]benzenemethanol	380
111	α-[[Methyl[[4-(4-methyl-3-thienyl)phenyl]methyl]amino]methyl]benzenemethanol	338
112	1-(2-Fluoro-4-nitrophenoxy)-3-[[[3-fluoro-2'-(trifluoromethyl)[1,1'-biphenyl]-4-yl]methyl]methylamino]-2-propanol	497
113	1-[[[3-Fluoro-2'-(trifluoromethyl)[1,1'-biphenyl]-4-yl]methyl]methylamino]-3-(4-nitrophenoxy)-2-propanol	479
114	1-(4-Fluorophenoxy)-3-[[[3-fluoro-2'-(trifluoromethyl)[1,1'-biphenyl]-4-yl]methyl]methylamino]-2-propanol	452
115	α-[[[[3-Fluoro-2'-(trifluoromethyl)[1,1'-biphenyl]-4-yl]methyl]methylamino]methyl]benzenemethanol	404
116	2-Fluoro-α-[[[[3-fluoro-2'-(trifluoromethyl)[1,1'-biphenyl]-4-yl]methyl]methylamino]methyl]benzenemethanol	422
117	4-Chloro-α-[[[[3-fluoro-2'-(trifluoromethyl)[1,1'-biphenyl]-4-yl]methyl]methylamino]methyl]benzenemethanol	438
118	1-[[[2-Chloro-2'-(trifluoromethyl)[1,1'-biphenyl]-4-yl]methyl]methylamino]-3-(2-fluoro-4-nitrophenoxy)-2-propanol	513
119	1-[[[2-Chloro-2'-(trifluoromethyl)[1,1'-biphenyl]-4-yl]methyl]methylamino]-3-(4-nitrophenoxy)-2-propanol	495
120	1-[[[2-Chloro-2'-(trifluoromethyl)[1,1'-biphenyl]-4-yl]methyl]methylamino]-3-(4-fluorophenoxy)-2-propanol	468
121	α-[[[[2-Chloro-2'-(trifluoromethyl)[1,1'-biphenyl]-4-yl]methyl]methylamino]methyl]benzenemethanol	420

Example No.	Compound Name	MS (ESI) $(M+H)^+$
122	α-[[[[2-Chloro-2'-(trifluoromethyl)[1,1'-biphenyl]-4-yl]methyl]methylamino]methyl]-2-fluorobenzenemethanol	438
123	4-Chloro-α-[[[[2-chloro-2'-(trifluoromethyl)[1,1'-biphenyl]-4-yl]methyl]methylamino]methyl]benzenemethanol	454
124	α-[[[(2-Chloro[1,1'-biphenyl]-4-yl)methyl]methylamino]methyl]benzenemethanol	352
125	1-[[(2'-Chloro-5'-methoxy[1,1'-biphenyl]-4-yl)methyl]methylamino]-3-(2-fluoro-4-nitrophenoxy)-2-propanol	475
126	1-[[(2'-Chloro-5'-methoxy[1,1'-biphenyl]-4-yl)methyl]methylamino]-3-(4-nitrophenoxy)-2-propanol	457
127	1-[[(2'-Chloro-5'-methoxy[1,1'-biphenyl]-4-yl)methyl]methylamino]-3-(4-fluorophenoxy)-2-propanol	430
128	α-[[[(2'-Chloro-5'-methoxy[1,1'-biphenyl]-4-yl)methyl]methylamino]methyl]benzenemethanol	382
129	α-[[[(2'-Chloro-5'-methoxy[1,1'-biphenyl]-4-yl)methyl]methylamino]methyl]-2-fluorobenzenemethanol	400
130	4-Chloro-α-[[[(2'-chloro-5'-methoxy[1,1'-biphenyl]-4-yl)methyl]methylamino]methyl]benzenemethanol	416
131	α-[[[(2'-Chloro-5'-methoxy[1,1'-biphenyl]-4-yl)methyl]methylamino]methyl]-4-(trifluoromethyl)benzenemethanol	450
132	α-[[Methyl[[5-[2-(trifluoromethyl)phenyl]-2-furanyl]methyl]amino]methyl]benzenemethanol	376

What is claimed is:

1. A compound of formula I or a pharmaceutically acceptable salt thereof:



I

wherein

Ar^1 is arylene, heteroarylene, substituted arylene or substituted heteroarylene, wherein a ring atom of Ar^1 connected to Ar^2 is seperated from a ring atom of Ar^1 connected to X by at least one atom;

Ar^2 is aryl, heteroaryl, substituted aryl or substituted heteroaryl;

n is 0 or 1;

X is a divalent group that separates groups connected thereto by one or two atoms;

R^1 is a monovalent C_{1-20} group comprising one or more heteroatoms selected from S, O, N and P;

R^2 is hydrogen, C_{1-10} alkyl, C_{1-10}acyl, substituted C_{1-10}acyl, substituted C_{1-10} alkyl, C_{1-10} alkylene, or substituted C_{1-10} alkylene, wherein said alkylene is linked to a ring carbon of Ar^1.

2. A compound of claim 1, wherein

Ar^1 is an arylene, heteroarylene, substituted arylene or substituted heteroarylene, wherein a ring atom of Ar^1 connected to Ar^2 is seperated from a ring atom of Ar^1 connected to X by at least one atom;

Ar^2 is an aryl, heteroaryl, substituted aryl or substituted heteroaryl;

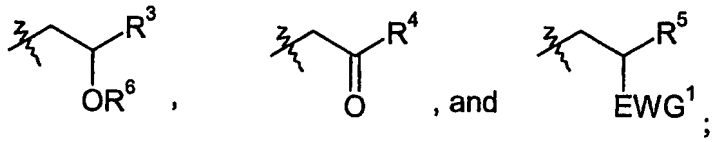
X is $-CH_2-$, or $-CH_2-CH_2-$;

R^2 is C_{1-6} alkyl, substituted C_{1-6} alkyl, C_{1-3} alkylene, or substituted C_{1-3} alkylene, wherein said alkylene is linked to a ring carbon of Ar^1.

3. A compound of claim 2,

wherein

R^1 is selected from:



wherein R^3 is optionally hydrogen, substituted C_{1-10}alkyl, optionally substituted C_{5-12}aryl, optionally substituted C_{3-10}heteroaryl, optionally substituted aryloxy-C_{1-6}alkyl, optionally substituted heteroaryloxy-C_{1-6}alkyl;

R^4 and R^5 are, independently, hydrogen, optionally substituted C_{1-10}alkyl, optionally substituted C_{5-12}aryl, optionally substituted C_{3-10}heteroaryl, amino group, -NHC(=O)-O-R^7, or -NHC(=O)-R^7, wherein R^7 is C_{1-6}alkyl or aryl;

R^6 is hydrogen, optionally substituted C_{1-6}alkyl, or optionally substituted aryl; and

EWG^1 is an electron withdrawing group.

4. A compound according to claim 1, wherein

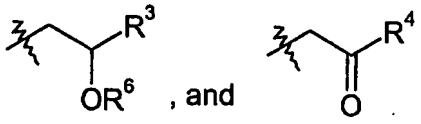
Ar^1 is optionally substituted *para*-phenylene, optionally substituted six-membered *para*-heteroarylene, or optionally substituted monocyclic five-membered *meta*-heteroarylene;

Ar^2 is optionally substituted phenyl, or optionally substituted monocylic five or six-membered heteroaryl;

X is $-CH_2-$, or $-CH_2-CH_2-$;

R^2 is C_{1-3} alkyl, substituted C_{1-3} alkyl, C_{1-3} alkylene, or substituted C_{1-3} alkylene, wherein said alkylene is linked to a ring carbon of Ar^1.

R^1 is selected from:



wherein R^3 is optionally substituted C_{1-6}alkyl, optionally substituted phenyl, optionally substituted phenoxy-methyl;

R^4 is, independently, optionally substituted C_{1-6}alkyl, optionally substituted phenyl, amino, -NHC(=O)-O-R^7, or -NHC(=O)-R^7, wherein R^7 is C_{1-6}alkyl or phenyl; and

R^6 is hydrogen, methyl or ethyl.

5. A compound according to claim 1, wherein

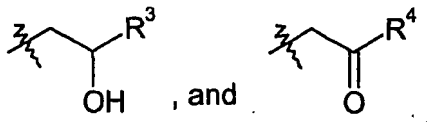
Ar^1 is *para*-phenylene or *para*-pyridylene;

Ar^2 is a phenyl *ortho*-substituted with an electron withdrawing group, or a thienyl *ortho*-substituted with an electron withdrawing group;

X is $-CH_2-$;

R^2 is methyl.

R^1 is selected from:



,

wherein R^3 is optionally substituted phenyl, or optionally substituted phenoxymethyl; and

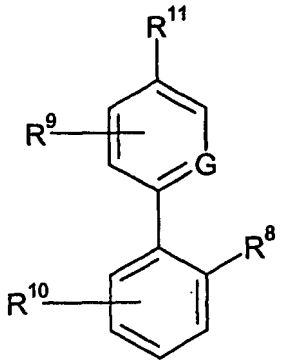
R^4 is $-NHC(=O)-O-R^7$, wherein R^7 is C_{1-6}alkyl.

6. A compound according to claim 5, wherein

Ar^2 is a phenyl *ortho*-substituted with -Cl, -F, -OMe, -OEt, $-O-CH(CH_3)_2$, $-CF_3$, $-NO_2$, or -CN; or thienyl *ortho*-substituted with -Cl, -F, -OMe, -OEt, $-O-CH(CH_3)_2$, $-CF_3$, $-NO_2$, -CN, wherein said *ortho*-subsituted Ar^2 is optionally further substituted at its non-*ortho* position; and

R^3 is phenyl, substituted phenoxymethyl or substituted phenyl.

7. A compound of formula II, or a pharmaceutically acceptable salt thereof:



II

wherein

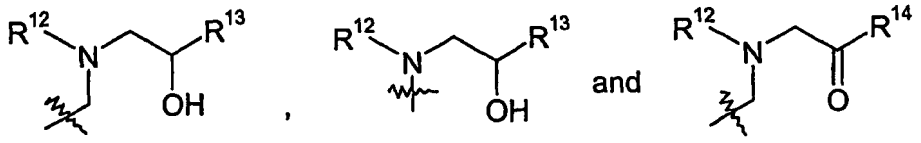
G is N or CH;

R^8 is selected from –H, $-CH_3$, $-CF_3$, $-NO_2$ and –CN;

R^9 is selected from –H and C_{1-3}alkyl;

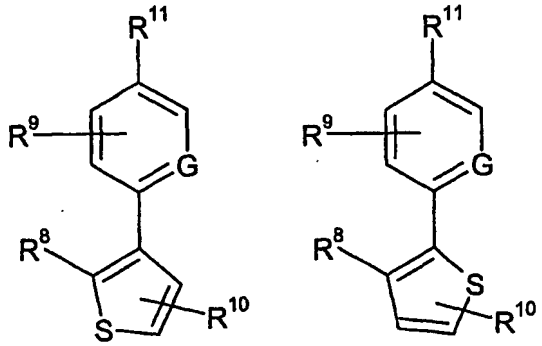
R^{10} is selected from –H and C_{1-3}alkyl; and

R^{11} is selected from



wherein R^{12} is H or methyl, R^{13} is phenyl or substituted phenoxymethyl, R^{14} is $-NHC(=O)OR^{15}$, wherein R^{15} is C_{1-6}alkyl.

8. A compound of formula III or IV, or a pharmaceutically acceptable salt thereof:



III IV

wherein

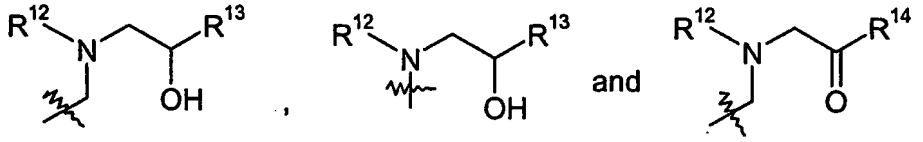
G is N or CH;

R^8 is selected from –H, $-CH_3$, $-CF_3$, $-NO_2$ and –CN;

R^9 is selected from –H and C_{1-3}alkyl;

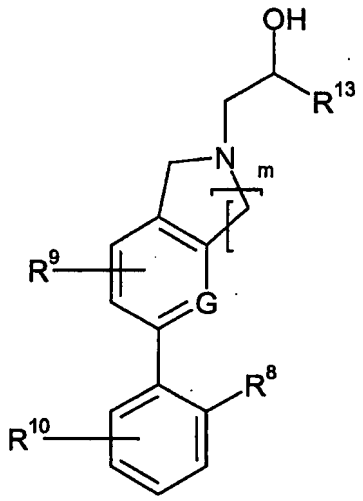
R^{10} is selected from –H and C_{1-3}alkyl; and

R^{11} is selected from



wherein R^{12} is H or methyl, R^{13} is phenyl or substituted phenoxymethyl, R^{14} is $-NHC(=O)OR^{15}$, wherein R^{15} is C_{1-6}alkyl.

9. A compound of formula V, or a pharmaceutically acceptable salt thereof:



V

wherein

G is N or CH;

m is 1 or 2;

R^8 is selected from –H, $-CH_3$, $-CF_3$, $-NO_2$ and –CN;

R^9 is selected from –H and C_{1-3}alkyl;

R^{10} is selected from –H and C_{1-3}alkyl; and

R^{13} is phenyl or substituted phenoxymethyl.

10. A compound is selected from:

α-[[Methyl[(2'-methyl[1,1'-biphenyl]-4-yl)methyl]amino]methyl]-benzenemethanol;

α-[[[(2'-Methoxy[1,1'-biphenyl]-4-yl)methyl]methylamino]methyl]-benzenemethanol;

α-[[[(2'-Chloro[1,1'-biphenyl]-4-yl)methyl]methylamino]methyl]-benzenemethanol;

α-[[Methyl-[[2'-(trifluoromethyl)-[1,1'-biphenyl]-4-yl]methyl]amino]methyl]-benzenemethanol;

1-(3,4-Dichlorophenoxy)-3-[methyl[[2'-(trifluoromethyl)[1,1'-biphenyl]-4-yl]methyl]amino]- 2-propanol;

α-[(2-Fluoro-4-nitrophenoxy)methyl]-3,4-dihydro-6-[2-(trifluoromethyl)phenyl]-2(1*H*)-isoquinolineethanol;

Ethyl [[methyl-[[2'-(trifluoromethyl)-[1,1'-biphenyl]-4-yl]methyl]amino]-acetyl]carbamate;

3,4-Dihydro-α-phenyl-7-[2-(trifluoromethyl)phenyl]-2(1*H*)-isoquinolineethanol;

1-(2-Fluoro-4-nitrophenoxy)-3-[methyl[2'-(trifluoromethyl)[1,1'-biphenyl]-4-yl]amino]- 2-propanol;

α-[(2-Fluoro-4-nitrophenoxy)methyl]-1,3-dihydro-5-[2-(trifluoromethyl)phenyl]-2*H*-isoindole-2-ethanol;

1-(2-Fluoro-4-nitrophenoxy)-3-[methyl[[2'-(trifluoromethyl)[1,1'-biphenyl]-4-yl]methyl]amino]- 2-propanol;

α-[[Methyl-[[6-[2-(trifluoromethyl)phenyl]-3-pyridinyl]methyl]amino]methyl]-benzenemethanol;

α-[[Methyl[(2'-nitro[1,1'-biphenyl]-4-yl)methyl]amino]methyl]-benzenemethanol;

(α^1S)-α-[[Methyl[[2'-(trifluoromethyl)[1,1'-biphenyl]-4-yl]methyl]amino]methyl]-benzenemethanol;

(α^1R)-α-[[Methyl[[2'-(trifluoromethyl)[1,1'-biphenyl]-4-yl]methyl]amino]methyl]-benzenemethanol;

α-[[Methyl[[2-methyl-2'-(trifluoromethyl)[1,1'-biphenyl]-4-yl]methyl]amino]methyl]-benzenemethanol;

N-(2-Hydroxy-2-phenylethyl)-*N*-[[2'-(trifluoromethyl)[1,1'-biphenyl]-4-yl]methyl]acetamide;

N-(2-Hydroxy-2-phenylethyl)-*N*-methyl-2'-(trifluoromethyl)-[1,1'-biphenyl]-4-carboxamide;

β-Methoxy-*N*-methyl-*N*-[[2'-(trifluoromethyl)[1,1'-biphenyl]-4-yl]methyl]-benzeneethanamine;

3,4-Dihydro-α-phenyl-6-[2-(trifluoromethyl)phenyl]-2(1*H*)-isoquinolineethanol;

α-[[Methyl[[5-[1-methyl-5-(trifluoromethyl)-1*H*-pyrazol-3-yl]-2-thienyl]methyl]amino]methyl]-benzenemethanol;

1-(2-Fluoro-4-nitrophenoxy)-3-[methyl[[2'-(trifluoromethyl)[1,1'-biphenyl]-4-yl]methyl]amino]-2-propanol ;

1-[Methyl[[2'-(trifluoromethyl)[1,1'-biphenyl]-4-yl]methyl]amino]-3-(4-nitrophenoxy)-2-propanol;

1-[[(2',3'-Dimethyl[1,1'-biphenyl]-4-yl)methyl]methylamino]-3-(2-fluoro-4-nitrophenoxy)-2-propanol;

α-[[Methyl-[[2'-(trifluoromethyl)-[1,1'-biphenyl]-4-yl]methyl]amino]methyl]-benzenemethanol;

4-Chloro-α-[[[(2'-chloro[1,1'-biphenyl]-4-yl)methyl]methylamino]methyl]-benzenemethanol;

1-[[(2',5'-Dimethyl[1,1'-biphenyl]-4-yl)methyl]methylamino]-3-(2-fluoro-4-nitrophenoxy)-2-propanol;

α-[[[(2',5'-Dimethyl[1,1'-biphenyl]-4-yl)methyl]methylamino]methyl]-benzenemethanol;

α-[[Methyl[[4-(3-methyl-2-thienyl)phenyl]methyl]amino]methyl]-benzenemethanol;

1-[4-(1,1-Dimethylethyl)phenoxy]-3-[methyl[[2'-(trifluoromethyl)[1,1'-biphenyl]-4-yl]methyl]amino]-2-propanol;

1-[4-(1,1-Dimethylethyl)phenoxy]-3-[[(2'-methoxy[1,1'-biphenyl]-4-yl)methyl]methylamino]-2-propanol;

β-Ethoxy-*N*-methyl-*N*-[[2'-(trifluoromethyl)[1,1'-biphenyl]-4-yl]methyl]benzeneethanamine;

N-Methyl-*N*-[[2'-(trifluoromethyl)[1,1'-biphenyl]-4-yl]methyl]glycylglycine, ethyl ester;

N-Ethyl-2-[methyl[[2'-(trifluoromethyl)[1,1'-biphenyl]-4-yl]methyl]amino]acetamide;

α-[(2-Fluoro-4-nitrophenoxy)methyl]-3,4-dihydro-7-[2-(trifluoromethyl)phenyl]-2(1*H*)-isoquinolineethanol;

α-[[Methyl[(2,2',5'-trimethyl[1,1'-biphenyl]-4-yl)methyl]amino]methyl]benzenemethanol;

1-[[[2'-Chloro-5'-(trifluoromethyl)[1,1'-biphenyl]-4-yl]methyl]methylamino]-3-(2-fluoro-4-nitrophenoxy)-2-propanol;

4'-[[[3-(2-Fluoro-4-nitrophenoxy)-2-hydroxypropyl]methylamino]methyl]-6-methoxy-[1,1'-biphenyl]-3-carbonitrile;

1-[[(2',5'-Dichloro[1,1'-biphenyl]-4-yl)methyl]methylamino]-3-(2-fluoro-4-nitrophenoxy)-2-propanol;

1-[[[4-(2-Chloro-3-thienyl)phenyl]methyl]methylamino]-3-(2-fluoro-4-nitrophenoxy)-2-propanol;

4'-[[[3-(2-Fluoro-4-nitrophenoxy)-2-hydroxypropyl]methylamino]methyl]-[1,1'-biphenyl]-2-carbonitrile;

1-[[(2'-Chloro-5'-methyl[1,1'-biphenyl]-4-yl)methyl]methylamino]-3-(2-fluoro-4-nitrophenoxy)-2-propanol;

1-[[(5'-Chloro-2'-methyl[1,1'-biphenyl]-4-yl)methyl]methylamino]-3-(2-fluoro-4-nitrophenoxy)-2-propanol;

1-(2-Fluoro-4-nitrophenoxy)-3-[methyl[(2'-nitro[1,1'-biphenyl]-4-yl)methyl]amino]-2-propanol;

α-[[[[4-(2-Chloro-3-thienyl)phenyl]methyl]methylamino]methyl]benzenemethanol;

4'-[[(2-Hydroxy-2-phenylethyl)methylamino]methyl]- [1,1'-biphenyl]-2-carbonitrile;

α-[[[(5'-Chloro-2'-methyl[1,1'-biphenyl]-4-yl)methyl]methylamino]methyl]benzenemethanol;

α-[[Methyl[[2'-methyl-5'-(trifluoromethyl)[1,1'-biphenyl]-4-yl]methyl]amino]methyl]benzenemethanol;

α-[[[[2'-Chloro-5'-(trifluoromethyl)[1,1'-biphenyl]-4-yl]methyl]methylamino]methyl]benzenemethanol;

4'-[[(2-Hydroxy-2-phenylethyl)methylamino]methyl]-6-methoxy-[1,1'-biphenyl]-3-carbonitrile;

α-[[[(2'-Fluoro[1,1'-biphenyl]-4-yl)methyl]methylamino]methyl]benzenemethanol;

α-[[[(2',5'-Dichloro[1,1'-biphenyl]-4-yl)methyl]methylamino]methyl]-benzenemethanol;

Methyl 3-[4-[[(2-hydroxy-2-phenylethyl)methylamino]methyl]phenyl]-2-thiophenecarboxylate;

α-[[Methyl[[2'-(1-methylethoxy)[1,1'-biphenyl]-4-yl]methyl]amino]methyl]benzenemethanol;

α-[[[(2'-Ethoxy[1,1'-biphenyl]-4-yl)methyl]methylamino]methyl]benzenemethanol;

α-[[Methyl[[2'-(2-propenyl)[1,1'-biphenyl]-4-yl]methyl]amino]methyl]benzenemethanol;

α-[[[(2'-Cyclopentyl[1,1'-biphenyl]-4-yl)methyl]methylamino]methyl]benzenemethanol;

α-[[Methyl[[5'-methyl-2'-(1-methylethyl)[1,1'-biphenyl]-4-yl]methyl]amino]methyl]benzenemethanol;

α-[[[(2'-Methoxy-5'-methyl[1,1'-biphenyl]-4-yl)methyl]methylamino]methyl]-benzenemethanol;

1-(2-Fluoro-4-nitrophenoxy)-3-[methyl[[2'-methyl-5'-(trifluoromethyl)[1,1'-biphenyl]-4-yl]methyl]amino]-2-propanol;

α-[[[[5-(4-Bromophenyl)-2-furanyl]methyl]methylamino]methyl]benzenemethanol;

α-[[[[5-(4-Chlorophenyl)-2-furanyl]methyl]methylamino]methyl]benzenemethanol;

α-[[Methyl[[5-[3-(trifluoromethyl)phenyl]-2-furanyl]methyl]amino]methyl]benzenemethanol;

Methyl 3-[5-[[(2-hydroxy-2-phenylethyl)methylamino]methyl]-2-furanyl]-2-thiophenecarboxylate;

α-[[Methyl[[4-(3-pyridinyl)phenyl]methyl]amino]methyl]benzenemethanol;

1-[[(2'-Chloro[1,1'-biphenyl]-4-yl)methyl]methylamino]-3-[4-(1,1-dimethylethyl)phenoxy]-2-propanol;

1-(4-Chlorophenoxy)-3-[methyl[[2'-(trifluoromethyl)[1,1'-biphenyl]-4-yl]methyl]amino]-2-propanol;

1-[Methyl[[2'-(trifluoromethyl)[1,1'-biphenyl]-4-yl]methyl]amino]-3-phenoxy-2-propanol;

1-[[(2'-Methoxy[1,1'-biphenyl]-4-yl)methyl]methylamino]-3-(4-nitrophenoxy)-2-propanol;

α-[[Methyl[[2'-(trifluoromethyl)[1,1'-biphenyl]-4-yl]methyl]amino]methyl]benzeneethanol;

1-(1,1-Dimethylethoxy)-3-[methyl[[2'-(trifluoromethyl)[1,1'-biphenyl]-4-yl]methyl]amino]-2-propanol;

Methyl 2-hydroxy-2-methyl-3-[methyl[[2'-(trifluoromethyl)[1,1'-biphenyl]-4-yl]methyl]amino]propanoate;

(β¹S)-β-[[(2'-Chloro[1,1'-biphenyl]-4-yl)methyl]methylamino]-cyclohexanepropanol;

1-(4-Chlorophenoxy)-3-[[(2'-methyl[1,1'-biphenyl]-4-yl)methyl]-2-propenylamino]-2-propanol;

1-[[(2'-Methyl[1,1'-biphenyl]-4-yl)methyl]-2-propenylamino]-3-phenoxy-2-propanol;

1-[[(2'-Chloro[1,1'-biphenyl]-4-yl)methyl]-2-propenylamino]-3-phenoxy-2-propanol;

1-Phenoxy-3-[2-propenyl[[2'-(trifluoromethyl)[1,1'-biphenyl]-4-yl]methyl]amino]-2-propanol;

1-[[(2'-Chloro[1,1'-biphenyl]-4-yl)methyl]-2-propenylamino]-3-(3,4-dichlorophenoxy)-2-propanol;

1-[([1,1'-Biphenyl]-4-ylmethyl)-2-propenylamino]-3-(4-nitrophenoxy)-2-propanol;

1-[[(2'-Methyl[1,1'-biphenyl]-4-yl)methyl]-2-propenylamino]-3-(4-nitrophenoxy)-2-propanol;

1-[[(2'-Chloro[1,1'-biphenyl]-4-yl)methyl]-2-propenylamino]-3-(4-nitrophenoxy)-2-propanol;

1-(4-Nitrophenoxy)-3-[2-propenyl[[2'-(trifluoromethyl)[1,1'-biphenyl]-4-yl]methyl]amino]-2-propanol;

(α^1S)-α-[[[(2'-Methyl[1,1'-biphenyl]-4-yl)methyl]-2-propenylamino]methyl]benzenemethanol;

(α^1S)-α-[[[(2'-Chloro[1,1'-biphenyl]-4-yl)methyl]-2-propenylamino]methyl]benzenemethanol;

(2*R*)-3-[[(2'-Chloro[1,1'-biphenyl]-4-yl)methyl]-2-propenylamino]-2-hydroxypropyl butanoate ;

(2*R*)-2-Hydroxy-3-[2-propenyl[[2'-(trifluoromethyl)[1,1'-biphenyl]-4-yl]methyl]amino]propyl butanoate;

Methyl 2-hydroxy-2-methyl-3-[2-propenyl[[2'-(trifluoromethyl)[1,1'-biphenyl]-4-yl]methyl]amino]propanoate;

1-(3-Fluoro-4-nitrophenoxy)-3-[methyl[[2'-(trifluoromethyl)[1,1'-biphenyl]-4-yl]methyl]amino]-2-propanol;

1-(4-Iodophenoxy)-3-[methyl[[2'-(trifluoromethyl)[1,1'-biphenyl]-4-yl]methyl]amino]-2-propanol;

1-(3-Fluorophenoxy)-3-[methyl[[2'-(trifluoromethyl)[1,1'-biphenyl]-4-yl]methyl]amino]-2-propanol;

Ethyl 4-[2-hydroxy-3-[methyl[[2'-(trifluoromethyl)[1,1'-biphenyl]-4-yl]methyl]amino]propoxy]-benzenecarboximidate;

1-[[(2'-Chloro[1,1'-biphenyl]-4-yl)methyl]methylamino]-3-(3-fluoro-4-nitrophenoxy)-2-propanol;

1-[[(2'-Chloro[1,1'-biphenyl]-4-yl)methyl]methylamino]-3-(2-fluoro-4-nitrophenoxy)-2-propanol;

1-[[(2'-Chloro[1,1'-biphenyl]-4-yl)methyl]methylamino]-3-(4-nitrophenoxy)-2-propanol;

1-[[(2',3'-Dimethyl[1,1'-biphenyl]-4-yl)methyl]methylamino]-3-phenoxy-2-propanol;

1-[[(2',3'-Dimethyl[1,1'-biphenyl]-4-yl)methyl]methylamino]-3-(4-nitrophenoxy)-2-propanol;

N,N-Diethyl-4-[3-[[(5'-fluoro-2'-methyl[1,1'-biphenyl]-4-yl)methyl]methylamino]-2-hydroxypropoxy]-3-methoxybenzamide;

Ethyl 4-[3-[[(5'-fluoro-2'-methyl[1,1'-biphenyl]-4-yl)methyl]methylamino]-2-hydroxypropoxy]benzenecarboximidate;

4-[3-[[[4'-Chloro-2'-(trifluoromethyl)[1,1'-biphenyl]-4-yl]methyl]methylamino]-2-hydroxypropoxy]-*N*,*N*-diethyl-3-methoxybenzamide;

2-[3-[[[4'-Chloro-2'-(trifluoromethyl)[1,1'-biphenyl]-4-yl]methyl]methylamino]-2-hydroxypropoxy]benzamide;

1-[[[4'-Chloro-2'-(trifluoromethyl)[1,1'-biphenyl]-4-yl]methyl]methylamino]-3-(3-methoxyphenoxy)-2-propanol;

1-[[[4'-Chloro-2'-(trifluoromethyl)[1,1'-biphenyl]-4-yl]methyl]methylamino]-3-(1*H*-indol-5-yloxy)-2-propanol;

Ethyl 4-[3-[[[4'-chloro-2'-(trifluoromethyl)[1,1'-biphenyl]-4-yl]methyl]methylamino]-2-hydroxypropoxy]benzenecarboximidate;

1-[[[4'-Chloro-2'-(trifluoromethyl)[1,1'-biphenyl]-4-yl]methyl]methylamino]-3-phenoxy-2-propanol;

1-[[[4'-Chloro-2'-(trifluoromethyl)[1,1'-biphenyl]-4-yl]methyl]methylamino]-3-(4-nitrophenoxy)-2-propanol;

2-Fluoro-α-[[methyl[[2'-(trifluoromethyl)[1,1'-biphenyl]-4-yl]methyl]amino]methyl]benzenemethanol;

α-[[[(2'-Chloro[1,1'-biphenyl]-4-yl)methyl]methylamino]methyl]-2-fluorobenzenemethanol;

α-[[[(2'-Chloro-6'-methyl[1,1'-biphenyl]-4-yl)methyl]methylamino]methyl]benzenemethanol;

α-[[[(2',5'-Dimethyl[1,1'-biphenyl]-4-yl)methyl]methylamino]methyl]-2-fluorobenzenemethanol;

4-Chloro-α-[[[(2',5'-dimethyl[1,1'-biphenyl]-4-yl)methyl]methylamino]methyl]benzenemethanol;

α-[[Methyl[[4-(4-methyl-3-thienyl)phenyl]methyl]amino]methyl]benzenemethanol;

1-(2-Fluoro-4-nitrophenoxy)-3-[[[3-fluoro-2'-(trifluoromethyl)[1,1'-biphenyl]-4-yl]methyl]methylamino]-2-propanol;

1-[[[3-Fluoro-2'-(trifluoromethyl)[1,1'-biphenyl]-4-yl]methyl]methylamino]-3-(4-nitrophenoxy)-2-propanol;

1-(4-Fluorophenoxy)-3-[[[3-fluoro-2'-(trifluoromethyl)[1,1'-biphenyl]-4-yl]methyl]methylamino]-2-propanol;

α-[[[[3-Fluoro-2'-(trifluoromethyl)[1,1'-biphenyl]-4-yl]methyl]methylamino]methyl]benzenemethanol;

2-Fluoro-α-[[[[3-fluoro-2'-(trifluoromethyl)[1,1'-biphenyl]-4-yl]methyl]methylamino]methyl]benzenemethanol;

4-Chloro-α-[[[[3-fluoro-2'-(trifluoromethyl)[1,1'-biphenyl]-4-yl]methyl]methylamino]methyl]benzenemethanol;

1-[[[2-Chloro-2'-(trifluoromethyl)[1,1'-biphenyl]-4-yl]methyl]methylamino]-3-(2-fluoro-4-nitrophenoxy)-2-propanol;

1-[[[2-Chloro-2'-(trifluoromethyl)[1,1'-biphenyl]-4-yl]methyl]methylamino]-3-(4-nitrophenoxy)-2-propanol;

1-[[[2-Chloro-2'-(trifluoromethyl)[1,1'-biphenyl]-4-yl]methyl]methylamino]-3-(4-fluorophenoxy)-2-propanol;

α-[[[[2-Chloro-2'-(trifluoromethyl)[1,1'-biphenyl]-4-yl]methyl]methylamino]methyl]benzenemethanol;

α-[[[[2-Chloro-2'-(trifluoromethyl)[1,1'-biphenyl]-4-yl]methyl]methylamino]methyl]-2-fluorobenzenemethanol;

4-Chloro-α-[[[[2-chloro-2'-(trifluoromethyl)[1,1'-biphenyl]-4-yl]methyl]methylamino]methyl]benzenemethanol;

α-[[[(2-Chloro[1,1'-biphenyl]-4-yl)methyl]methylamino]methyl]benzenemethanol;

1-[[(2'-Chloro-5'-methoxy[1,1'-biphenyl]-4-yl)methyl]methylamino]-3-(2-fluoro-4-nitrophenoxy)-2-propanol;

1-[[(2'-Chloro-5'-methoxy[1,1'-biphenyl]-4-yl)methyl]methylamino]-3-(4-nitrophenoxy)-2-propanol;

1-[[(2'-Chloro-5'-methoxy[1,1'-biphenyl]-4-yl)methyl]methylamino]-3-(4-fluorophenoxy)-2-propanol;

α-[[[(2'-Chloro-5'-methoxy[1,1'-biphenyl]-4-yl)methyl]methylamino]methyl]benzenemethanol;

α-[[[(2'-Chloro-5'-methoxy[1,1'-biphenyl]-4-yl)methyl]methylamino]methyl]-2-fluorobenzenemethanol;

4-Chloro-α-[[[(2'-chloro-5'-methoxy[1,1'-biphenyl]-4-yl)methyl]methylamino]methyl]benzenemethanol;

α-[[[(2'-Chloro-5'-methoxy[1,1'-biphenyl]-4-yl)methyl]methylamino]methyl]-4-(trifluoromethyl)benzenemethanol;

α-[[Methyl[[5-[2-(trifluoromethyl)phenyl]-2-furanyl]methyl]amino]methyl]benzenemethanol; and pharmaceutically acceptable salts thereof.

11. A compound according to any one of claims 1-10 for use as a medicament.

12. The use of a compound according to any one of claims 1-10 in the manufacture of a medicament for the therapy of pain.

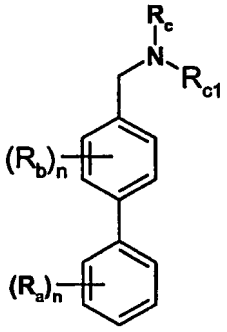
13. The use of a compound according to any one of claims 1-10 in the manufacture of a medicament for the treatment of immune cancer.

14. The use of a compound according to any one of claims 1-10 in the manufacture of a medicament for the treatment of multiple sclerosis, vision impairment, Parkinson's disease, Huntington's chorea or Alzheimer's disease.

15. A pharmaceutical composition comprising a compound according to any one of claims 1-10 and a pharmaceutically acceptable carrier.

16. A method for the therapy of pain in a warm-blooded animal, comprising the step of administering to said animal in need of such therapy a therapeutically effective amount of a compound according to any one of claims 1-10.

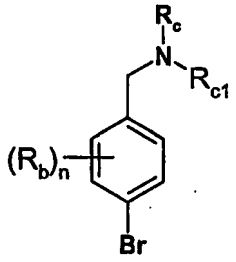
17. A method for preparing a compound of formula X,

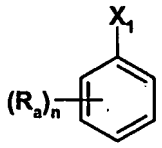


X

comprising the steps of

a) reacting a compound of formula IX with bis(pinacolato)diboron in the presence of $Pd(PPh_3)_4$; and

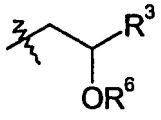




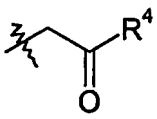
IX , VI

b) reacting a product of step a) with a compound of formula VI to form the compound of formula X,

wherein R_a and R_b are independently selected from –H, C_{1-6}alkyl, $-CF_3$, $-NO_2$, and –CN; n is 1 or 2; R_c is selected from:



, and

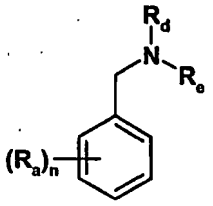


,

wherein R^3 is optionally substituted phenyl, or optionally substituted phenoxy-methyl;

R^4 is -NHC(=O)-O-R^7, wherein R^7 is C_{1-6}alkyl; and R_{c1} is –H or C_{1-3}alkyl.

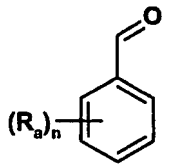
18. A process for preparing a compound of formula XIII,



XIII

comprising the steps of:

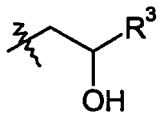
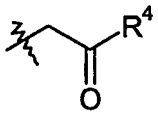
a) reacting a compound of formula XI with R_dR_eNH; and



XI ,

b) reacting a product of step a) with $NaBH(OAc)_3$ to form the compound of formula XIII,

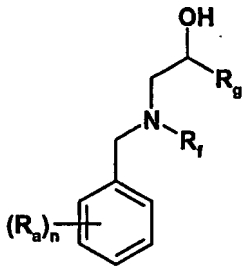
R_a is selected from optionally subsituted aryl, optionally subsituted heteroaryl; n is 1 or 2; R_d and R_e are independently selected from –H, C_{1-3}alkyl,

 , and  ,

wherein R^3 is optionally substituted phenyl, or optionally substituted phenoxy-methyl,

R^4 is -NHC(=O)-O-R^7, wherein R^7 is C_{1-6}alkyl; wherein at least one of R_d and R_e contains an oxygen atom.

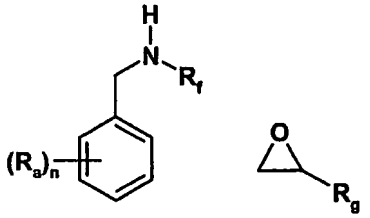
19. A method for preparing a compound of formula XV,



XV

comprising the step of:

reacting a compound of formula XII with a compound of formula XIV,



XII , XIV ,

wherein R_a is selected from optionally substituted aryl and optionally substituted heteroaryl; n is 1 or 2; R_f is –H or C_{1-3}alkyl; and R_g is optionally subsitituted phenyl or optionally subsituted phenoxymethyl.

5

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE 2003/002088

A. CLASSIFICATION OF SUBJECT MATTER

IPC7: C07D 333/10, C07D 213/36, C07D 211/70, C07D 209/44, C07C 221/27, A61K 31/137, A61K 31/4035 A61K 31/4418, 31/451, 31/381, A61P 25/04

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC7: C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

SE,DK,FI,NO classes as above

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

CHEM.ABS.DATA, WPI DATA, BIOSIS

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	Chemistry and Physics of Lipids, Volume 121, 2002, Sonya L. Palmer et al, "Review: Cannabinergic ligands", pages 3-19 ---	1-19
A	Chemistry and Physics of Lipids, Volume 121, 2002, T. Philip Malan et al, "Review: Inhibition of pain responses by activation of CB2 cannabinoid receptors", pages 191-200 --- --------	1-19

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"B" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance: the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance: the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
5 April 2004	08-04-2004
Name and mailing address of the ISA/ Swedish Patent Office Box 5055, S-102 42 STOCKHOLM Facsimile No. +46 8 666 02 86	Authorized officer CAROLINA GÓMEZ LAGERLÖF/BS Telephone No. +46 8 782 25 00

Form PCT/ISA/210 (second sheet) (January 2004)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE 2003/002088

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: 16
because they relate to subject matter not required to be searched by this Authority, namely:

see extra sheet

2. ☒ Claims Nos.: 1-6
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

see extra sheet

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE 2003/002088

Box II.1

Claim 16 relate to methods of treatment of the human or animal body by surgery or by therapy or diagnostic methods practiced on the human or animal body (Rule 39.1(iv)). Nevertheless, a search has been executed for this claim. The search has been based on the alleged effects of the compounds or compositions.

Box II.2

Present claims 1-6 relate to a large number of possible compounds. Support within the meaning of Article 6 PCT is to be found, however, for only a very small proportion of the compounds claimed. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible.
Consequently, the search has been carried out for those parts of the claims which appear to be supported and disclosed, namely those parts related to the compounds defined in claims 7-9.

US005812123A

United States Patent [19]

Rowe et al.

[11] Patent Number: 5,812,123

[45] Date of Patent: *Sep. 22, 1998

[54] **SYSTEM FOR DISPLAYING PROGRAMMING INFORMATION**

[75] Inventors: **Keith Rowe**; **Frank Lawler**, both of Seattle; **Joseph H. Matthews, III**, Redmond, all of Wash.

[73] Assignee: **Microsoft Corporation**, Redmond, Wash.

[*] Notice: The term of this patent shall not extend beyond the expiration date of Pat. No. 5,623,613.

[21] Appl. No.: **766,808**

[22] Filed: **Dec. 13, 1996**

Related U.S. Application Data

[63] Continuation of Ser. No. 346,422, Nov. 29, 1994, Pat. No. 5,623,613.

[51] **Int. Cl.**[6] **G06F 15/00**

[52] **U.S. Cl.** **345/327**; 345/146; 345/341; 345/353; 345/354

[58] **Field of Search** 395/352, 353, 395/354, 356, 357; 345/327, 328, 340, 341, 146

[56] **References Cited**

U.S. PATENT DOCUMENTS

5,485,618 1/1996 Smith 345/338

FOREIGN PATENT DOCUMENTS

WO 92/04801 3/1992 WIPO .

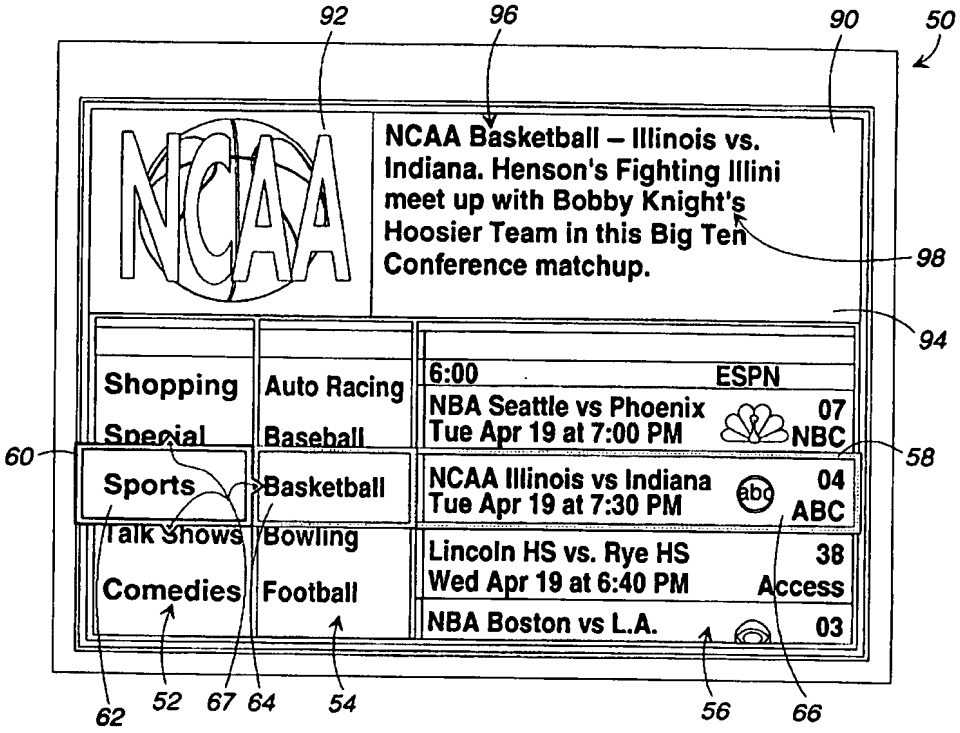
Primary Examiner—Huynh Ba

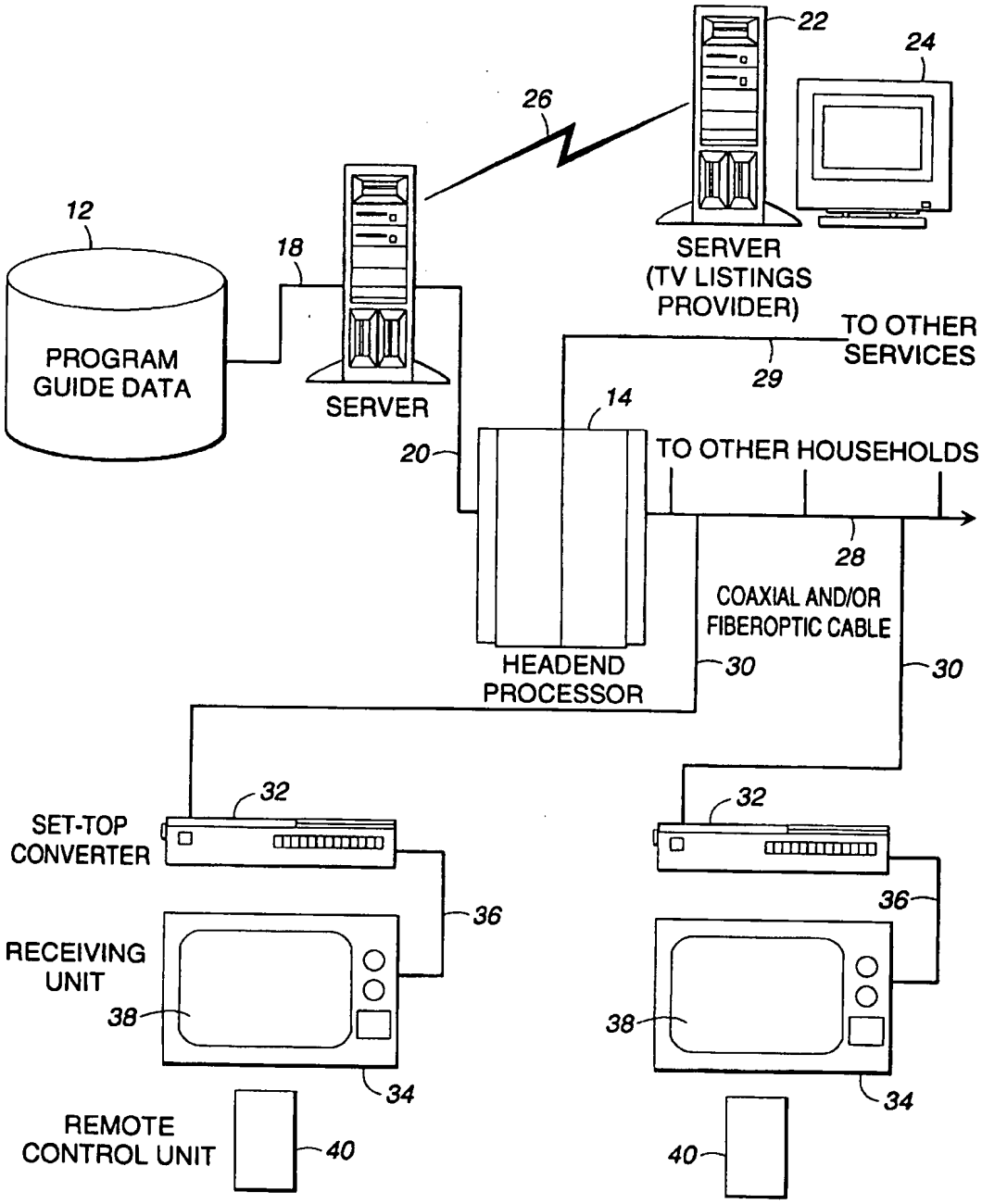
Attorney, Agent, or Firm—Jones & Askew, LLP

[57] **ABSTRACT**

A system for retrieving and displaying programming information in response to selection of a category of programming information. Programming information is presented via a schedule display having a category display, a subcategory category display, and a program display. The category display displays an array of category tiles representing categories of programming information. The subcategory display displays an array of subcategory tiles representing subcategories that are associated with the categories of the category display. The program display displays an array of program tiles that are associated with the subcategories of the subcategory display. A viewing panel extends along each of the displays for displaying one each of the category, subcategory, and program tiles. Classes of programming information are selected by scrolling the tiles of the associated displays until the desired class items are presented within the viewing panel.

37 Claims, 6 Drawing Sheets




22
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12
18
PROGRAM GUIDE DATA
SERVER
SERVER (TV LISTINGS PROVIDER)
TO OTHER SERVICES
29
14
20
TO OTHER HOUSEHOLDS
28
COAXIAL AND/OR FIBEROPTIC CABLE
HEADEND PROCESSOR
30
30
32
32
SET-TOP CONVERTER
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RECEIVING UNIT
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REMOTE CONTROL UNIT
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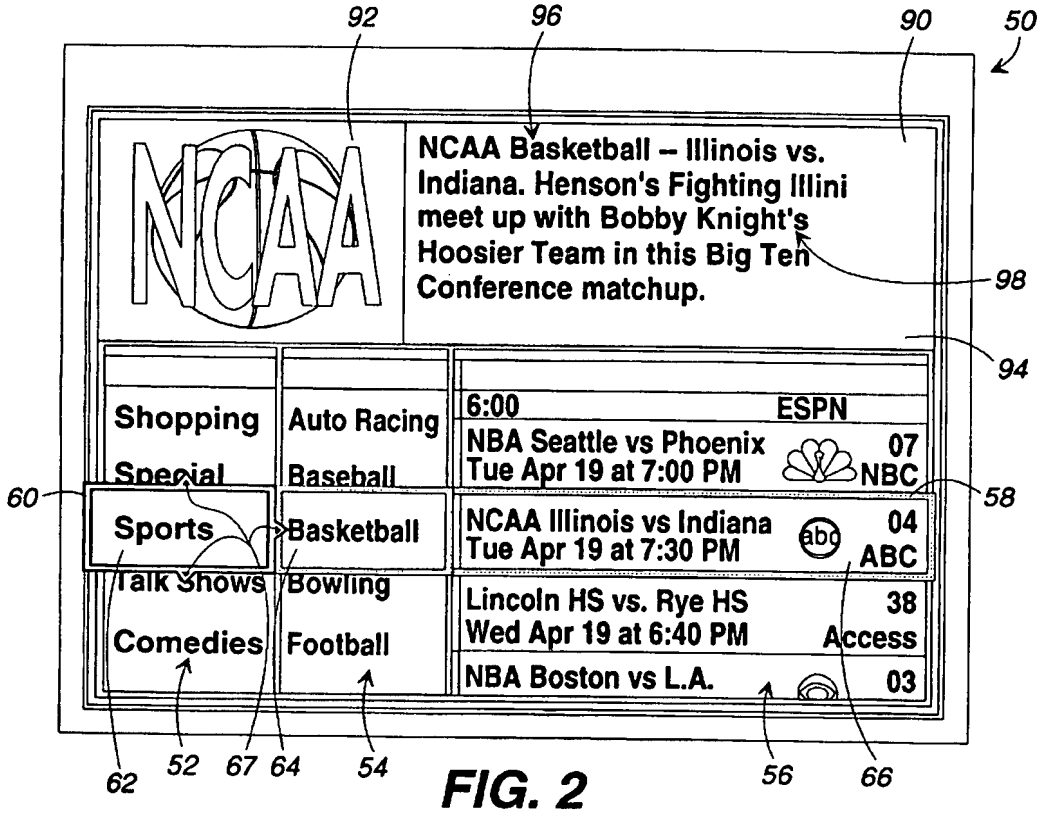
FIG. 1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NCAA Basketball – Illinois vs. Indiana. Henson's Fighting Illini meet up with Bobby Knight's Hoosier Team in this Big Ten Conference matchup.
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Special
Sports
Talk Shows
Comedies
Auto Racing
Baseball
Basketball
Bowling
Football
6:00 ESPN
NBA Seattle vs Phoenix 07
Tue Apr 19 at 7:00 PM NBC
NCAA Illinois vs Indiana 04
Tue Apr 19 at 7:30 PM ABC
Lincoln HS vs. Rye HS 38
Wed Apr 19 at 6:40 PM Access
NBA Boston vs L.A. 03
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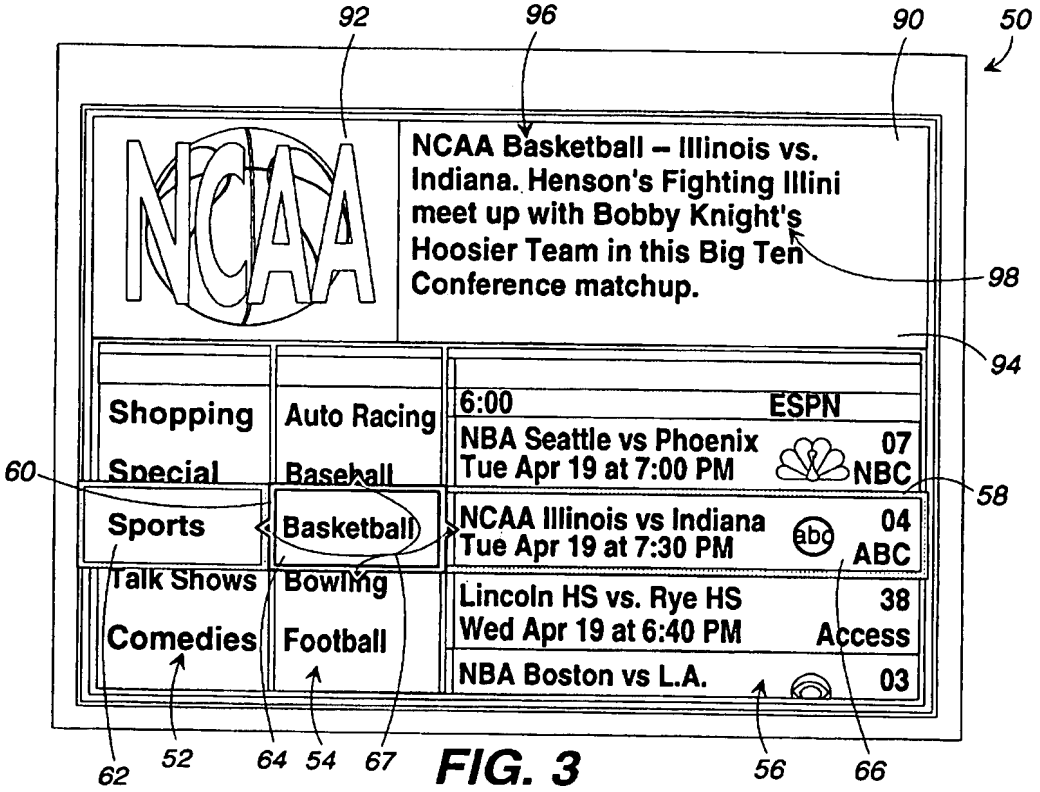
FIG. 2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NCAA Basketball – Illinois vs. Indiana. Henson's Fighting Illini meet up with Bobby Knight's Hoosier Team in this Big Ten Conference matchup.
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Special
Sports
Talk Shows
Comedies
Auto Racing
Baseball
Basketball
Bowling
Football
6:00 ESPN
NBA Seattle vs Phoenix 07
Tue Apr 19 at 7:00 PM NBC
NCAA Illinois vs Indiana 04
Tue Apr 19 at 7:30 PM ABC
Lincoln HS vs. Rye HS 38
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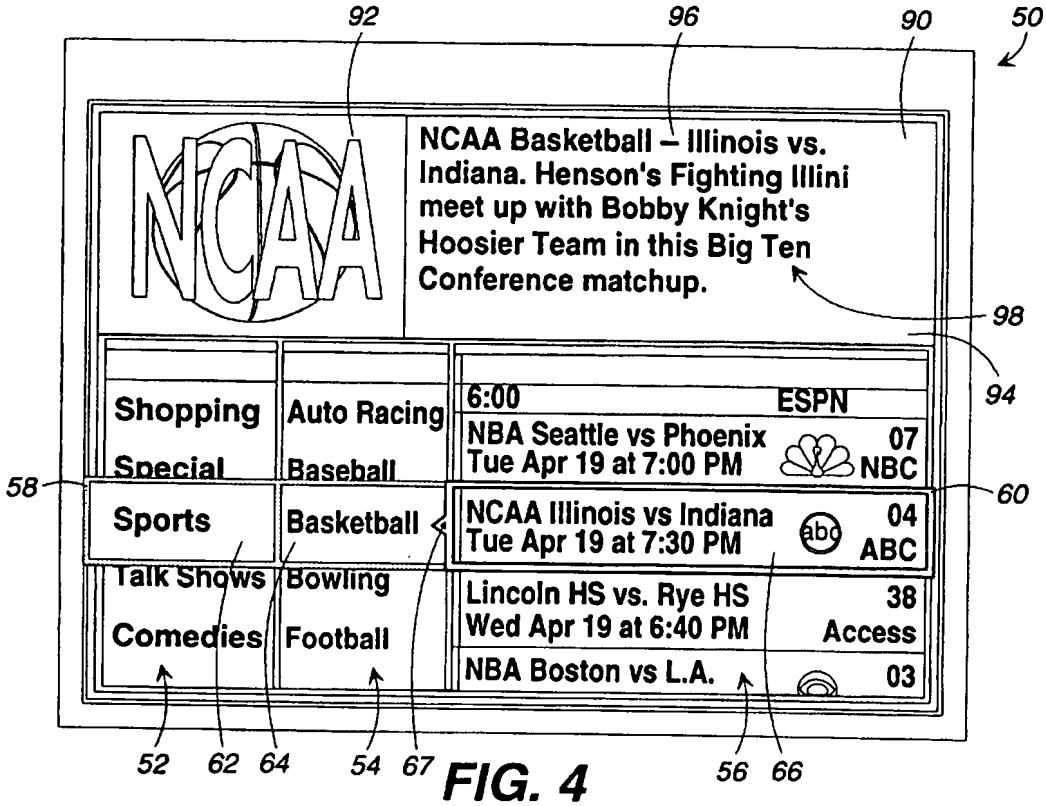
FIG. 3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NCAA Basketball – Illinois vs. Indiana. Henson's Fighting Illini meet up with Bobby Knight's Hoosier Team in this Big Ten Conference matchup.
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Auto Racing
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NBA Seattle vs Phoenix 07
Tue Apr 19 at 7:00 PM NBC
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Sports
Basketball
NCAA Illinois vs Indiana 04
Tue Apr 19 at 7:30 PM ABC
60
Talk Shows
Comedies
Bowling
Football
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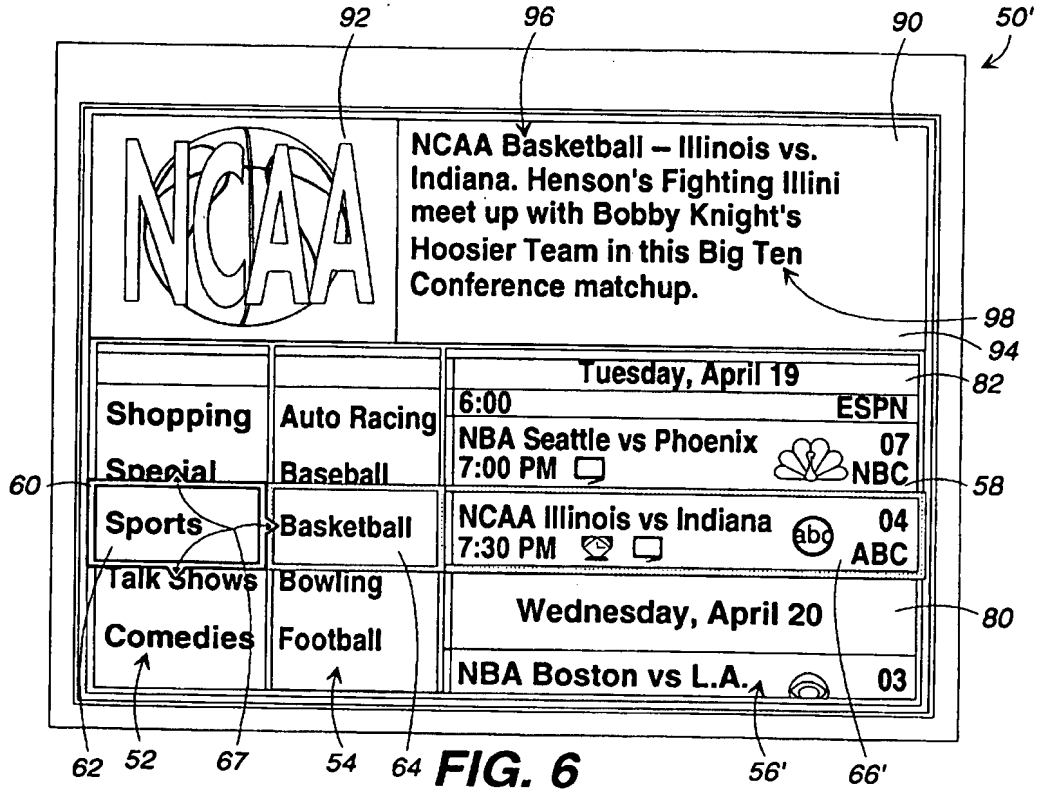
FIG. 4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7:00 PM NBC
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Basketball
NCAA Illinois vs Indiana 04
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FIG. 6

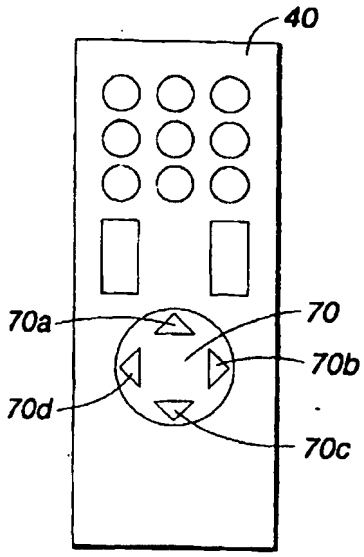
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FIG. 5

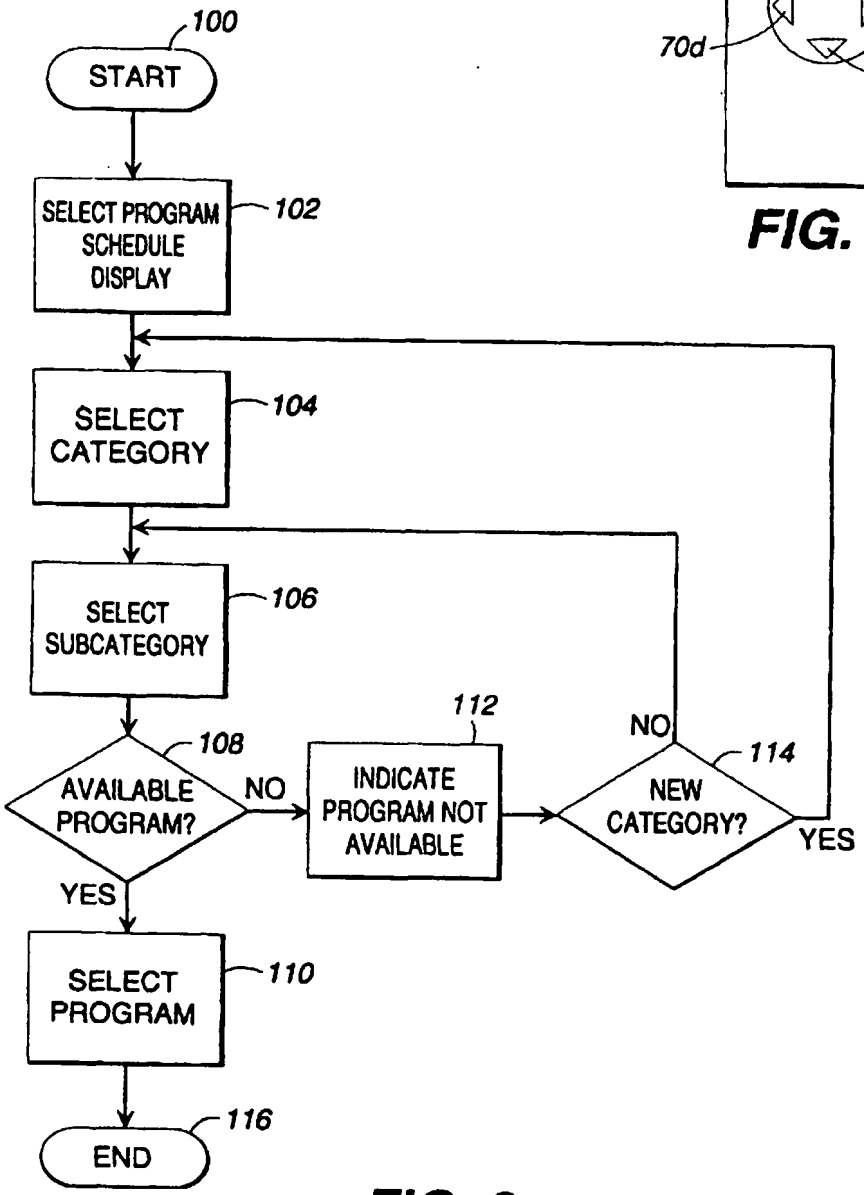
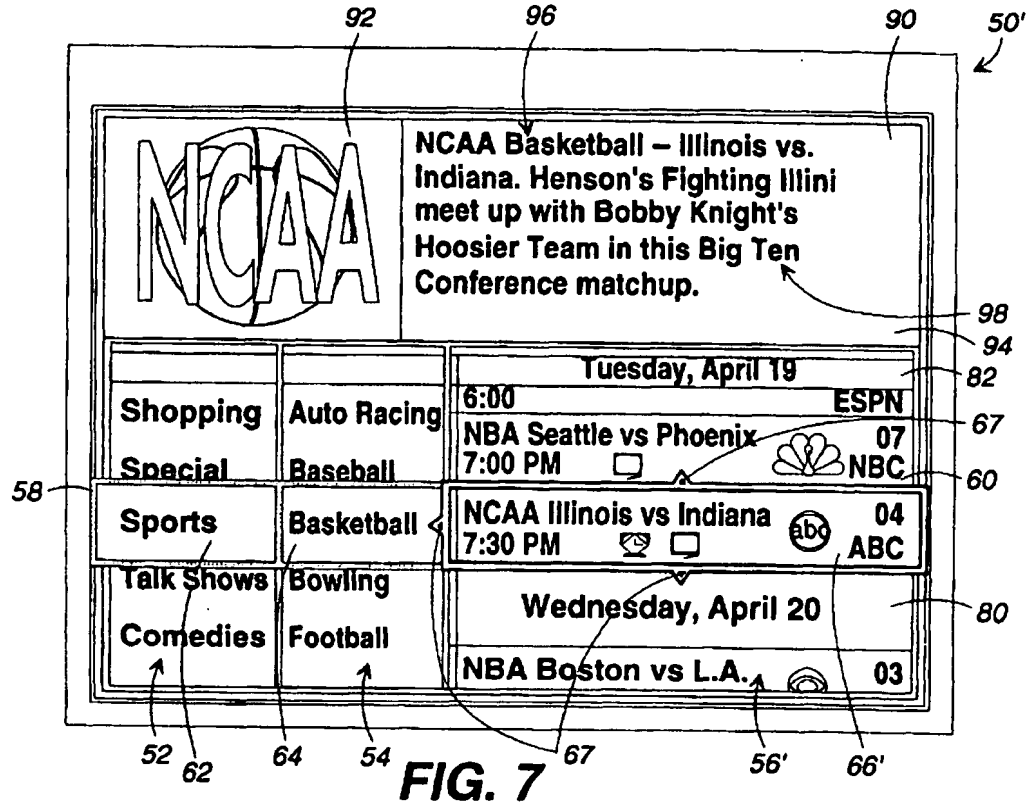

100
START
SELECT PROGRAM SCHEDULE DISPLAY
102
SELECT CATEGORY
104
SELECT SUBCATEGORY
106
AVAILABLE PROGRAM?
108
NO
INDICATE PROGRAM NOT AVAILABLE
112
NEW CATEGORY?
114
NO
YES
YES
SELECT PROGRAM
110
END
116

FIG. 9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82
Tuesday, April 19
6:00 ESPN
NBA Seattle vs Phoenix 07
7:00 PM NBC
67
60
58
Shopping
Special
Auto Racing
Baseball
Sports
Basketball
NCAA Illinois vs Indiana 04
7:30 PM ABC
Talk Shows
Comedies
Bowling
Football
Wednesday, April 20
80
NBA Boston vs L.A. 03
52
62
64
54
67
56'
66'

FIG. 7

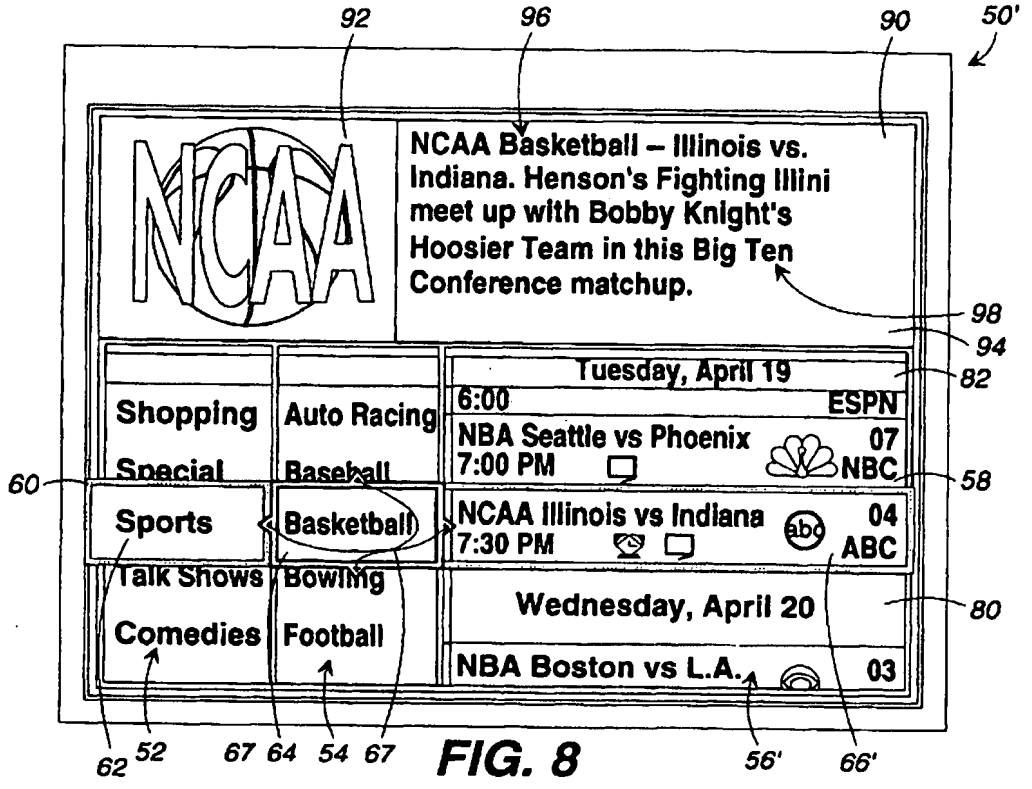
92
96
90
50'
NCAA Basketball – Illinois vs. Indiana. Henson's Fighting Illini meet up with Bobby Knight's Hoosier Team in this Big Ten Conference matchup.
98
94
82
Tuesday, April 19
6:00 ESPN
NBA Seattle vs Phoenix 07
7:00 PM NBC
60
58
Shopping
Special
Auto Racing
Baseball
Sports
Basketball
NCAA Illinois vs Indiana 04
7:30 PM ABC
Talk Shows
Comedies
Bowling
Football
Wednesday, April 20
80
NBA Boston vs L.A. 03
62
52
67
64
54
67
56'
66'

FIG. 8

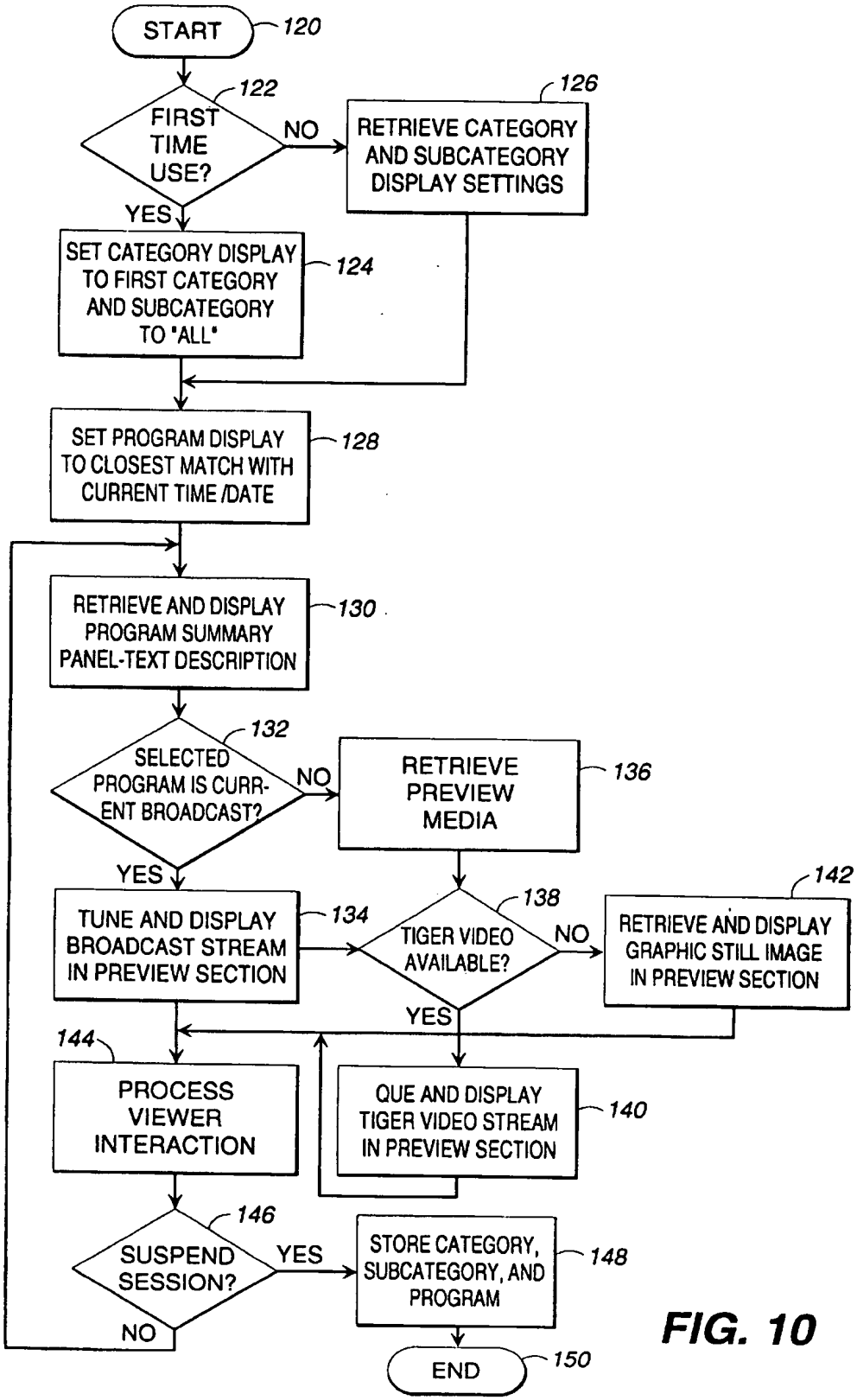
START
120
FIRST TIME USE?
122
NO
RETRIEVE CATEGORY AND SUBCATEGORY DISPLAY SETTINGS
126
YES
SET CATEGORY DISPLAY TO FIRST CATEGORY AND SUBCATEGORY TO "ALL"
124
SET PROGRAM DISPLAY TO CLOSEST MATCH WITH CURRENT TIME /DATE
128
RETRIEVE AND DISPLAY PROGRAM SUMMARY PANEL-TEXT DESCRIPTION
130
SELECTED PROGRAM IS CURR-ENT BROADCAST?
132
NO
RETRIEVE PREVIEW MEDIA
136
YES
TUNE AND DISPLAY BROADCAST STREAM IN PREVIEW SECTION
134
TIGER VIDEO AVAILABLE?
138
NO
RETRIEVE AND DISPLAY GRAPHIC STILL IMAGE IN PREVIEW SECTION
142
YES
144
PROCESS VIEWER INTERACTION
QUE AND DISPLAY TIGER VIDEO STREAM IN PREVIEW SECTION
140
SUSPEND SESSION?
146
YES
STORE CATEGORY, SUBCATEGORY, AND PROGRAM
148
NO
END
150

FIG. 10

SYSTEM FOR DISPLAYING PROGRAMMING INFORMATION

This is a continuation of application Ser. No. 08/346,422, entiled "System for Displaying Programming Information," filed Nov. 29, 1994 on behalf of the inventors, Keith Rowe, Frank Lawler, and Joseph H. Matthews, III, now U.S. Pat. No. 5,623,613.

TECHNICAL FIELD

The invention relates generally to schedules for programming information and, more specifically, to a system for retrieving and displaying programming information in response to selection of a category of programming information.

BACKGROUND OF THE INVENTION

A national information infrastructure constructed from both wireless and wired communications networks supports the communication of information in homes and businesses throughout the country. Telephones, televisions, radios, computers, and facsimile machines are used each day to receive, store, process, perform, display, and transmit data, text, voice, sound, and graphic images. These devices are typically connected via fiber optic cables, coaxial cables, electronic switches and routers, microwave networks, satellites, and other communications technologies. This national information infrastructure, which may one day be expanded to a global infrastructure, supports the electronic transfer of a wide variety of programming to entertain, instruct, or inform receiving parties. In view of both the variety and the substantial amount of available programming, a user typically uses a programming schedule or guide to select a desired program for reception (or transmission) on a certain date and time.

For example, a subscriber to cable network programming services, such as premium cable television or audio services, typically uses a printed schedule to select a program for viewing or listening to at a certain time period. In addition, certain cable television services supply the viewer with an on-screen programming schedule from the headend processor via the cable distribution network. For both printed and on-screen programming schedules, the programming information is typically presented as a function of the date and time for the scheduled programs. Thus, if the subscriber is interested in viewing a sports-related program, it is necessary for the subscriber to review the time periods for that date to determine if a sports-related program is scheduled during the viewing period. This time-based presentation of programming schedule information is satisfactory only when the amount of available programming is relatively limited. Furthermore, unlike the printed programming schedule, the user typically cannot control the order of the programming information supplied by an on-screen programming schedule because this information is supplied from a remote location via a conventional one-way cable distribution network.

In view of the advances in computing and broadband communications systems, it is expected that the present information infrastructure will evolve into an integrated communications network supported by advanced high-speed, interactive, broadband, digital communications equipment. Telephones, televisions, radios, computers, and facsimile machines will be linked by this interactive broadband information infrastructure and will be able to communicate and interact with other communication devices in a digital signal format. This interactive broadband information infrastructure, commonly referred to as the "information superhighway," has great potential to increase access to information and entertainment resources that can be delivered quickly and economically anywhere in the country. For example, it is feasible that hundreds of channels of "television" programming, thousands of audio recordings, and literally millions of "magazines" and "books" can be made available to homes and businesses via this information superhighway. In view of this tremendous expansion of available programming, the use of a programming schedule or guide will be critical for a user to select a desired program. However, as choices of programming increase, the prior time-based format of programming schedules becomes a less manageable technique for choosing a desired program because of the numerous programs available for any one time period. Thus, there is a need for a category-based programming schedule to clarify and to simplify for an audience the process of selecting programs of interest to each audience member.

The present invention supplies a system of retrieving and displaying a schedule for programming based primarily upon the classes of programs, rather than the time period for each program. The programming information displayed by this system is restricted to those programs matching characteristics selected by the viewer. This permits the viewer to narrow the scope of programming information supplied by the system to a more manageable number of choices and enables the viewer to have personal control over the displayed programming information. The present invention also provides a highly intuitive user interface to support the easy and convenient selection of desired programming information.

SUMMARY OF THE INVENTION

The present invention fulfills the above-described needs by providing a system for presenting programming information in an efficient and user-friendly manner based upon the classes of scheduled programs. This allows a user to view programming information by genre groupings rather than by a time-based schedule, thereby affording the user the opportunity to obtain information about a desired program from a substantial listing of available programs. The programming schedule can be presented as a display on a display device, such as a television or a computer monitor. The user can control the displayed programming information by selecting the category for the desired program, thereby updating the displayed programming information to match the viewer's selection. The selection of programming information can be controlled remotely via a remote control unit or directly by another input device, such as a keypad or a touch-sensitive screen.

Generally described, the system for retrieving and displaying programming information, i.e., the programming guide system, presents scheduling information for programs via a schedule display having three display elements, a category display, a subcategory display, and a program display. The category display displays an array of category tiles representing categories of programming information. The subcategory display displays an array of subcategory tiles representing subcategories that are associated with the categories of the category display. The program display displays an array of program tiles representing programs that are associated with the subcategories of the subcategory display.

To allow the user to easily view the tiles of each of the displays, the displays can be located adjacent to each other.

A viewing panel can extend along a portion of each of the displays for displaying one each of the category, subcategory, and program tiles. In this manner, the viewer is presented with selected programming information divided into three separate classes, namely broad, mid, and narrow-scope classes of programming information.

A category of programming information can be selected by moving a corresponding category tile within the viewing panel. In response, the subcategory display displays a subcategory tile representing the subcategory associated with the selected category. This narrows the scope of displayed programming information by supplying subcategory information that is relevant to the selected category.

Likewise, a subcategory of programming information can be selected by moving the corresponding subcategory tile within the viewing panel. In response, the program display displays one or more program tiles representing programs associated with the selected subcategory. This further narrows the scope of displayed scheduling information to the level of individual programs. The program tiles representing these programs can be ordered chronologically to supply the viewer with a time-based view of programs associated with the selected subcategory and the selected category.

The programming information is stored within one or more databases and is retrievable to support the display of selected programming information by the display system. Specifically, the category tiles, subcategory tiles, and program tiles are stored within a database structure on a memory storage device and can be retrieved as required to support the display of programming information represented by these tiles. Thus, at least one of the subcategory tiles representing a subcategory associated with a selected category is retrieved from the database in response to a selected category tile appearing within the viewing panel. In response to a selected subcategory tile appearing within the viewing panel, at least one program tile representing a program associated with the selected subcategory is retrieved from the database if a program is available that is associated with the selected subcategory.

More particularly described, the user can peruse a selected class of programming information by scrolling the tiles of one of the category, subcategory, or program displays. To control the display of one of the category, subcategory, or program tiles, the user can move a focus frame along the viewing panel to a location proximate to the selected corresponding display. The focus frame operates to highlight information supplied by the tile selected by the user by "framing" the tile, and supplies a visual cue to the user that the display associated with the framed tile can be controlled. For example, to control the category display, the user moves the focus frame along the viewing panel to a position on the category display. Upon positioning the focus frame over the category display, the category tile appearing within the viewing panel also appears within the focus frame. Thus, the focus frame extends along the boundary of the selected category tile. For this position of the focus frame, the viewer can scroll in a selected direction the category tiles, thereby supporting the selection of another category tile for viewing within the viewing panel (and the focus frame). Similar to the representative example of the category display, each of the subcategory and program displays can be controlled by placing the focus frame proximate to the respective display and thereafter scrolling through the tiles representing the selected programming information.

A remote control unit, such as an infrared transmitting device, can be used to transmit commands for controlling the programming information displayed by the category, subcategory, and program displays. Specifically, the position of the focus frame can be changed or the tiles of a selected display can be scrolled by outputting appropriate directional instructions via the remote control unit, thereby allowing the viewer to navigate the sources of programming information. However, other types of input devices also can be used to control the category, subcategory, and program displays, including a direct-wired keypad or a touch-sensitive screen.

Each of the program tiles can include text-based and/or graphical information regarding the represented program, including name, program date and start-time, and program channel. In addition, a program tile can list the network responsible for supplying the program, including the logo or symbol for the responsible network. Another option for program tiles is the use of graphic images, such as information icons, to represent secondary program information, including the items of closed captioning, audience rating, awards, star rating, or rerun status. The use of information icons on a program tile reduces the amount of text displayed on the screen, which, in turn, makes it easier to locate and read program titles or names.

For another aspect of the present invention, the program display can include date tiles representing calendar dates to separate the time-sorted program tiles, thereby eliminating any requirement of supplying date-related information for each program tile. Each date tile can separate program tiles associated with one date from program tiles associated with another date. In this manner, the program tiles in the corresponding programs are grouped by both date and time. The program display also can include a date status indicator that displays the date associated with the presently displayed program tiles.

Accordingly, it is an object of the present invention to provide a system for retrieving and displaying programming information based upon the categories of the programming information.

It is a further object of the present invention to provide a system for retrieving and displaying a schedule for programming in response to program characteristics selected by the user.

It is a further object of the present invention to provide a system for retrieving and displaying programming information that allows the user to narrow the scope of displayed programming information to a more manageable number of program choices.

It is a further object of the present invention to provide a highly intuitive user interface for a programming guide system to support a simple and convenient selection of desired programming information.

The attainment of the foregoing and related objects, advantages, and features of the present invention will be more readily apparent after review of the detailed description to follow and the appended drawings.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. **1** is a block diagram of the operating environment for the preferred embodiment of the present invention.

FIGS. **2**, **3**, and **4** are representations of a programming schedule incorporating the user interface for the preferred embodiment of the present invention.

FIG. **5** is an illustration of the face of a remote control unit that supports the user's control of programming information displayed by the preferred embodiment of the present invention.

FIGS. 6, 7, and 8 are representations of an alternative programming schedule incorporating the user interface for another embodiment of the present invention.

FIG. 9 is a logical flow diagram illustrating the steps of the preferred method for retrieving and displaying programming information.

FIG. 10 is a logical flow diagram illustrating the steps of operation for a program schedule of the preferred embodiment of the present invention.

DETAILED DESCRIPTION

The present invention is directed to a system for retrieving and displaying programming information, thereby providing a user with a schedule or guide of available programs. Although the preferred embodiment of the present invention will be described with respect to interactive and broadcast television programming, those skilled in the art will recognize that the present invention can be used with other forms of programming information, including radio, broadcast print, audio, games, computer software, and other combinations of audio/video or software information. Accordingly, it will be understood that programming information generally includes information for programs transmitted electronically to entertain, instruct, or inform the recipient.

Turning now to the drawings, in which like numerals indicate like elements throughout the several figures, FIG. 1 illustrates the operating environment for the program schedule system 10. A memory storage device 12, such as a hard disk drive or an optical storage system, stores programming information in a digital format. This programming information can be supplied for the benefit of one or more subscribers to communications services responsible for the origination or distribution of programs associated with this programming information. One or more databases for various classes of programming information are maintained on the memory storage device 12.

For programming information related to television programs, the preferred database structure includes at least four tables, namely (1) a table containing records for each television episode, (2) a table containing records for each television series, (3) a table containing records of program categories, and (4) a table containing records of program subcategories. Each television episode is linked to its parent television series and each television series is associated with categories and subcategories which define the characteristics of the series. These categories and subcategories are respectively represented by the program category table and the program subcategory table, which are linked to records for the television series table by another table, the junction table. The junction table allows a one-to-many relationship, thereby supporting the classification of television programs under more than one category or subcategory.

To support the distribution of the programming information to each of the subscribers, the memory storage device 12 is connected to a headend processor 14 via a server 16. A conductive path 18 supplies a two-way communications link between the memory storage device 12 and the server 16. Likewise, a conductive path 20 supplies a two-way communications link between the headend processor 14 and the server 16. For the preferred embodiment, the server 16, in combination with the conductive paths 18 and 20, form a local area network that enables the headend processor 14 to interact with any other device on this network, including the memory storage device 12. The server 16 can be implemented by a computer running administrative software that controls access to the devices connected to the network.

To support the tasks of updating or revising the program information stored on the memory storage device 12, a computer workstation 24 and a server 22 are connected to the server 16 via a communications link 26. This communications link allows a program distributor or supplier, which typically operates at a location remote from the databases stored within the memory storage device 12, to transmit programming information for storage by the memory storage device 12 and eventual distribution to subscribers via the headend processor 14. The communications link 26 can be implemented by either a wireless or wired communications system. For example, the communications link 26 can be constructed as a microwave link or as a conventional telephone link.

The headend processor 14 operates to control the distribution of programming information stored on the memory storage device 12 and the associated programs to one or more subscribers of associated programming services. The headend processor 14 is connected to each of the subscribers via a cable distribution network 28. The cable distribution network 28 is preferably implemented as an interactive communications network. This supports delivery of programming information and programs via the headend processor 14 to the subscriber and the delivery of requests for programming information and programs by the subscriber to the headend processor 14. The cable distribution network 28 can be implemented by a microwave distribution system, a telephone system, coaxial or optical cables, or any combination of these delivery systems. The headend processor 14 also can support the distribution of programs associated with the programming information to the subscribers and support other services via a separate distribution network 29.

Those persons skilled in the art will appreciate that the programs delivered over the cable distribution network 28 typically comprise both video and audio signals. Programs can be delivered in digital format, analog format, or a combination of both analog and digital formats. However, for the preferred embodiment, the programs are delivered as a stream of digital video and audio signals. Likewise, programming information supplied to subscribers and requests or instructions issued by subscribers are preferably digital format signals.

Each subscriber is connected to the cable distribution network 28 via a cable 30 supplied to a set-top converter 32. The cable 30 is preferably implemented as either a coaxial cable or a fiber optic cable. In this manner, the subscriber "taps" into the cable distribution network 28 to (1) receive programs and programming information distributed by the headend processor 14 and to (2) transmit requests or instructions to the headend processor 14.

The set-top converter 32 accepts the programs and the programming information from the cable 30 and converts these signals to a format compatible for presentation by a receiving device 34, such as a television or a computer system. The set-top converter 32 is connected to the receiving device 34 via a conductive path 36. The receiving device 34 preferably includes a display 38 for displaying both programs and programming information. In particular, the programming information is supplied to the subscriber as a program schedule or guide via the display 38.

Selected operating functions of the set-top converter 32 can be remotely controlled by a remote control unit 40. The subscriber can use the remote control unit 40 to select for viewing certain characteristics of alternative user interfaces supplied by the schedule display, as described in more detail below with respect to FIGS. 2–4 and 6–8. The preferred remote control unit 40 is more fully described with respect to FIG. 5.

Generally, the instructions transmitted by the remote control unit **40** are received by the set-top converter **32** and, in response, one or more of the characteristics of the program schedule can be controlled to display the desired programming information to the subscriber. In particular, the set-top converter **32** receives certain instructions from the remote control unit **40** and, in turn, forwards these instructions to the headend processor **14** via the cable **30** and the cable distribution network **28**. The headend processor **14** responds by retrieving selected programming information from the memory storage device **12** and transmitting the selected programming information via the return path provided by the cable distribution network **28** and the cable **30**. The set-top converter **32** then supplies this programming information to update the schedule display presented by the display **38**.

FIG. **2** is a diagram illustrating the preferred presentation of programming information by a schedule display **50**. Referring to FIG. **2**, the schedule display **50** includes three display elements, a category display **52**, a subcategory display **54**, and a program display **56**. Each of the displays **52**, **54**, and **56** display separate classes of programming information. Specifically, the category display **52** displays various categories of programming information, such as "Animated," "Children," "Game Show," and so forth. Likewise, the subcategory display displays subcategories of programming information that are associated with the categories offered by the category display **52**. For example, subcategories for the "Animated" category can include "Adventure," "Children," or "Martial Arts." Thus, in comparison to the category display **52**, the subcategory display **54** displays a more narrow scope of programming information.

The program display **56** displays program items that are associated with the subcategories offered by the subcategory display **54**. Thus, the program display **56** supplies programming information that is narrower in scope than either the subcategories of the subcategory display **54** or the categories of category display **52**. For example, the program display **56** presents program-specific information, such as program title, program start-time, and program channel. Each of these program items represents an actual program that can be viewed by the subscriber at a certain date and time.

As shown in FIG. **2**, the displays **52**, **54**, and **56** are located adjacent to each other and the subcategory display **54** is sandwiched between the category display **52** and the program display **56**. A viewing panel **58** spans the width of the schedule display **50** by extending along a portion of each of the displays **52**, **54**, and **56**. For the preferred embodiment, the viewing panel **58** is mounted in a fixed location on the central portion of the schedule display **50**. In contrast, a focus frame **60**, which moves along a horizontal track of the viewing panel **58**, can be positioned proximate to any one of the displays **52**, **54**, and **56**. The viewing panel **58** focuses the subscriber's attention on a selected category, subcategory, and program. In contrast, the focus frame **60** serves to focus the user's attention upon a particular class of selected programming information and operates as an indication that the subscriber can control the programming information supplied by an associated display.

Programming information is presented by each of the displays **52**, **54**, and **56** via tiles, wherein each tile represents a specific item of programming information. The category display **52** includes category tiles **62** representing categories; the subcategory display **54** includes subcategory tiles **64** representing subcategories; and the program display **56** includes program tiles **66** representing programs. The category tiles **62** and the subcategory tiles **64** are preferably arranged in alphabetical order for the represented categories and subcategories. In contrast, the program tiles **66** are preferably chronologically-ordered based upon both the dates and start times of the represented programs.

The visible portion for each of the displays **52**, **54**, and **56**, i.e., the display panel, may reflect only a subset of the entire list of programming items represented by tiles. Accordingly, tiles which are not immediately visible to the subscriber can be accessed by scrolling the display in a selected vertical direction. By moving the tiles of the selected display in either an up or down direction, previously hidden tiles are revealed in one direction and previously visible tiles are obscured in the other direction. For example, the subcategory tiles **64** of the subcategory display **54** will wrap from beginning to end unless there are less than four items of programming information for the selected subcategory. Thus, each of the displays **52**, **54**, and **56** can be viewed as a vertically spinning dial of tiles that supply programming information.

To "spin" one of the displays **52**, **54**, or **56**, the focus frame **60** is moved along the viewing panel **58** to one of the displays. When the focus frame **60** is located proximate to the selected display, the subscriber has the option of scrolling up or down to reveal additional tiles. For the schedule display **50** shown in FIG. **2**, the focus frame **60** is located proximate to the category display **52**, thereby allowing the subscriber to scroll the category tiles **62** representing categories of programming information. FIGS. **3** and **4** respectively show the focus frame **60** located proximate to the subcategory display **54** and the program display **56**, thereby allowing the subscriber to control the items presented by these displays. For the preferred schedule display **50**, each of the displays **52**, **54**, and **56** uses three-dimensional shading to indicate that a tile is scrolling off beyond the visible area of its display.

As shown in FIGS. **2–4**, arrow tabs **67** can be appended to the sides of the focus frame **60** to supply the subscriber with an indication of (1) the direction(s) that the focus frame **60** can move along the viewing panel **58**, and (2) the directions that the subscriber can scroll the tiles of the selected display. For the schedule display **50** illustrated in FIG. **2**, an arrow tab **67** is appended to the right hand side of the focus frame **60** to supply the subscriber with an indication that the focus frame **60** can be moved to either the subcategory display **54** or the program display **56**. For this position of the focus frame **60**, arrow tabs **67** also can be appended to the top and bottom sides of the focus frame **60** to alert the subscriber that the category display **52** can be scrolled in the up direction or the down direction.

For the focus frame **60** located proximate to the subcategory display **54** in FIG. **3**, an arrow tab **67** can be appended to each of the four sides of the focus frame **60**, thereby advising the subscriber that the focus frame **60** can be moved in a horizontal direction to either the category display **52** or the program display **56**, and that the subcategory display **54** can be scrolled in either the up direction or the down direction. Likewise, for the focus frame **60** located proximate to the program display **56** shown in FIG. **4**, the focus frame **60** can include an arrow tab **67** located on the left hand side of the frame and arrow tabs **67** located on the top and bottom sides of the frame. The positioning of these arrow tabs **67** indicate that the subscriber can move the focus frame **60** along the viewing panel **58** to either the subcategory display **54** or the category display **52**, or scroll the program tiles in a selected vertical direction.

FIG. **5** is an illustration of the face of a remote control unit for controlling selected features of the schedule display.

Referring now to FIGS. **1**, **2** and **5**, the remote control unit **40** can transmit instructions to the set-top converter **32** to allow the subscriber to (1) move the focus frame **60** to one of the displays **52**, **54**, or **56**, and (2) scroll the tiles of the selected display. The face of the remote control unit **40** includes a control button **70** having navigation keys **70***a–d* for inputting commands to control features of the schedule display **50**. This control button **70** is preferably implemented as a rocker-type switch which can operated in four distinct positions represented by the navigation keys **70***a–d*. Navigation keys **70***b* and **70***d* control the position of the focus frame **60** along the viewing panel **58** and navigation keys **70***a* and **70***c* control the scrolling operations of the displays **52**, **54**, and **56**. Specifically, by pressing the navigation key **70***b*, the remote control unit **40** transmits a command to move the focus frame **60** to the right. In similar fashion, user selection of the navigation key **70***d* initiates a transmission of a command to move the focus frame **60** to the left. Navigation key **70***a* allows the subscriber to move the tiles of the selected display in an up direction, whereas navigation key **70***c* moves the tiles of the selected display in a down direction. The navigation keys **70***a–d* are preferably shaped in the form of an arrow to define the directional control functions associated with these command keys. The remote control unit **40** can include additional keys or buttons for inputting commands to control other operations of the set-top converter **32** or the receiving device **34**.

In response to a command input by one of the navigation keys **70***a–d*, the remote control unit **40** transmits an instruction to the set-top converter **32** via an infrared communications link. In turn, the set-top converter **32** decodes the instruction and responds by controlling the selected feature of the schedule display **50**. Specifically, the set-top converter **32**, which converts the programs and programming information delivered by the cable distribution network **28** for presentation via the display **38**, can control each of the displays **52**, **54**, and **56** and the position of the focus frame **60** on the viewing panel **58**. In addition, the set-top converter **32** can update the programming information presented by the schedule display **50** by outputting a request to the headend processor **14** via the return path supplied by the cable distribution network **28**. This allows the retrieval of desired programming information from the memory storage device **12** containing the database which maintains program guide data.

Returning now to FIGS. **1–4**, the subscriber typically selects programming information by first choosing the general category for the desired programming information. By moving the focus frame **60** to the category display **52**, the subscriber can select a category of programming information by scrolling the category display **52** until the category tile **62** representing the desired category appears within the viewing panel **58**. By scrolling the category tiles **62** in a selected vertical direction, each category tile sequentially appears within the viewing panel **58**. A category is selected when its corresponding category tile **62** appears within the frame of the viewing panel **58**. In turn, this "resets" the subcategory display **54** to display subcategory tiles **64** representing subcategories associated with the selected category. The program display **56** responds to the appearance of a selected subcategory tile **64** within the viewing panel **58** by displaying one or more program tiles **66** representing programs associated with the selected subcategory if such programs are available for the selected subcategory. Thus, the viewing panel **58** can display tiles representing the selected category, subcategory, and program.

In response to the selection of a new category of programming information, the set-top converter **32** outputs a request to the headend processor **14** for programming information representing subcategories associated with the selected category. The subcategory display **54** is reset by the set-top converter **32** in response to receiving the requested subcategory items over the cable distribution network **28**. Likewise, in response to the selection of a subcategory item, the set-top converter **32** outputs a request for programming information representing programs associated with the selected subcategory. If a program is available which corresponds to the selected subcategory and category, then the set-top converter **32** updates the program display **56** in response to receiving each program item via the cable distribution network **28**. This allows the programming information to be maintained at a central location, namely, the site of the memory storage device **12**, rather than in a memory device located within each set-top converter **32** at a subscriber's premises.

For a particular set of selected programming information, the viewing panel **58** preferably displays a single tile for each of the selected category display **52**, subcategory display **54**, and program display **56**. For example, the selected category for the schedule display **50** in FIGS. **2–4** is represented by the category tile **62** containing the text "Sports". Likewise, the selected subcategory is represented by the subcategory tile **64** containing the text "Basketball" and the selected program is represented by the program tile **66** containing the text "NCAA Illinois vs. Indiana". For this illustrated example, the user first selected the category of "Sports" and subsequently selected the associated subcategory of "Basketball" to obtain a listing of information for scheduled or available basketball-related programs. In view of the foregoing, it will be understood that the viewing panel supplies the user with a convenient viewing window for information items about an available program that is associated with the selected subcategory and category.

For the preferred embodiment of the schedule display **50**, neither the subcategory display **54** nor the program display **56** will change to reflect the selection of a new category until a short default time-out period has expired. This prevents rapid and unnecessary updating of these displays while the subscriber is navigating within the category display **52**. Accordingly, when a new category is selected by scrolling the corresponding category tile **62** within the viewing panel **58**, the "old" items displayed by the panels of the subcategory display **54** and program display **56** fade out and "new" items corresponding to the selected category fade in.

If a subcategory is selected and program-related information is not available, then the program display **56** becomes blank by failing to display any of the program tiles **66**. In addition, the right-hand side arrow tab **67** appended to the focus frame **60**, which is located proximate to the subcategory display **54**, is no longer shown to the user. Alternatively, the category display **52** and the subcategory display **54** can be restricted to respectively display tiles **62** and **64** for classes of programming information which represent available programs. These operations supply visual cues to the user that program-related information is not available for the selected subcategory that is represented by the subcategory tile **64** within the viewing panel **58**.

The preferred viewing panel **58** emphasizes the selection of the displayed items by highlighting the associated tiles within the frame of the viewing panel. This highlighting can be achieved by coloring or shading the tiles appearing within the viewing panel **58** in a color that is lighter than the remaining tiles displayed in the display panel for each of the displays **52**, **54**, and **56**. In addition, because the displays **52**, **54**, and **56** are located adjacent to each other, the selected category, subcategory, and program tiles **62**, **64**, and **66** are aligned within the viewing panel **58**. This presentation of the

programming information allows the subscriber to easily read the various classes of desired information by beginning with a broad genre on one side of the schedule display **50** and concluding with an individual program matching that genre on the other side of the schedule display **50**.

Table I supplies a representative list of categories and associated subcategories for the preferred system. The category tiles **62** and the subcategory tiles **64** respectively represent the items shown in the listings of Table I.

TABLE I

CATEGORY	SUBCATEGORIES
Animated	All
	Adventure
	Children
	Martial Arts
Awards	All
Children	All
	Science Fiction
	Action
	Adventure
	Animated
	Animals
	Anthology
	Comedy
	Drama
	Educational
	Exercise
	Fantasy
	Fiction
	Game Show
	Magazine
	Nature
	News
	Religious
	Science
	Spanish
	Sports
	Suspense
	Variety
Game Show	All
	Animals
	Educational
	Children
	Variety
Holiday	All
Magazine	All
	Auto
	Biography
	Educational
	Exercise
	Health
	How To
	Interview
	Children
	Medical
	Nature
	News
	Public Affairs
	Travel
Medical	All
	Health
Music	All
	Comedy
	Dance
	Drama
	Religious
	Travel
	Variety
Music	All
	Dance
	Religious
Musical	All
Soap Opera	All
	Comedy
	Drama
	Spanish
Sports Events	All

TABLE I-continued

CATEGORY	SUBCATEGORIES
	Event
	Anthology
	Baseball
	Boxing
	Basketball
	Bowling
	Golf
	Hockey
	Horse
	Racing
	Rodeo
	Rugby
	Soccer
	Track and Field
	Tennis
	Volleyball
	Wrestling
	Water
Sports Non-Event	All
	Action
	Adventure
	Auto
	Baseball
	Bicycle
	Biography
	Boat
	Body building
	Boxing
	Basketball
	Exercise
	Football
	Fishing
	Game Show
	Golf
	Hockey
	Horse
	How To
	Interview
	Magazine
	Martial Arts
	News
	Outdoors
	Racing
	Rodeo
	Rugby
	Running
	Softball
	Skiing
	Soccer
	Spanish
	Tennis
Sports Talk	All
	Baseball
	Basketball
	Interview
Talk	All
	Business
	Comedy
	Educational
	Fashion
	House and Garden
	Health
	Interview
	Magazine
	Medical
	Nature
	News
	Public Affairs
	Religious
	Science
	Self-Help
	Shopping
	Spanish
	Travel
	Variety

Referring to Table I, each subcategory having more than one item can include the special subcategory "All." The subcategory "All" encompasses all programming matching the associated category. This is preferably the default subcategory when the subscriber changes categories by selecting another category tile **62**, which, in turn, resets the subcategory display **54**. The remaining items within the listing of subcategories are directly linked to their respective category. For example, the subcategories "Business," "Comedy," and "Educational" are associated with the broad category of "Talk."

It will be appreciated that the present invention is not limited to the categories and subcategories listed in Table I, which is a listing of representative categories and associated subcategories of programming information. Those skilled in the art will understand that programming information can be divided into numerous broad and narrow classes and that the above-described system for retrieving and displaying programming information can be extended to other class-based listings of programming information. Accordingly, the listing in Table I is not intended to be a comprehensive list of possible categories and related subcategories of programming information.

Referring again to FIGS. **1–4**, the user can use the program display **56** to view program items for available programs which match the class items reflected in the display panels of the category display **52** and the subcategory display **54**. The program tiles **66** of the program display **56** are preferably displayed in sequential fashion based on the date and start time of the represented programs. For the preferred embodiment of the schedule display **50**, a program tile **66** representing programming information for a program available to the user on the present date is initially displayed within the viewing panel **58**. However, if the subscriber scrolls through the program tiles **66**, the subscriber can view in chronological order the various scheduled program items which match the selected category and subcategory. By convention, scrolling the program tiles **66** up allows a user to view program tiles **66**, if any, representing programs available to the user at a time later then the program represented by program tile **66** currently appearing within the viewing panel **58**. In contrast, scrolling the program tiles **66** down allows a user to view program tiles **66**, if any, representing programs available to the user at a time prior to the program associated with the program tile **66** currently appearing within the viewing panel **58**.

Each program tile **66** represents information about a selected program and can display the program title or name, the program date and start-time, and the channel number. Each program tile **66** also can include the network name and the network symbol, which is typically implemented as an icon graphically representing the logo of the corresponding channel or network. For example, the program tile **66** appearing within the viewing panel **58** in FIGS. **2–4** shows the program title "NCAA Illinois vs. Indiana," the name and symbol for the network "ABC", the channel number "04", and the date and start time "Tuesday April 19 at 7:30 PM." For the television application described herein, it will be appreciated that the programming information displayed by the program schedule generally corresponds to programs that are scheduled for the viewing benefit of the user.

For the preferred program display **56**, the program tiles **66** are sorted in chronological order and date and start time information are supplied by each program tile **66**.

The schedule display **50** also can include a program summary panel **90** to communicate detailed information about a selected program tile appearing within the viewing panel **58**. For the preferred embodiment, the program summary panel **90** is located near the top of the schedule display **50** and stretches horizontally along the top portion of each of the displays **52**, **54**, and **56**, thereby taking up approximately ⅓ of the schedule display **50**. The size of the program summary panel **90** is approximately 552×144 pixels. For the preferred schedule display **50**, the program summary panel **90** is always available for viewing by the user, regardless of the type or class of programming information selected by the user.

The information in the program summary panel **90** is preferably updated as the subscriber changes the settings of the schedule display **50**, i.e., changing a selected tile appearing within the viewing panel **58** by scrolling one of the category display **52**, subcategory display **54**, or program display **56**. This information update occurs in response to a "new" tile appearing within the viewing panel **58** and the expiration of a default time-out period. The default time-out period prevents rapid and unnecessary updating of the program summary panel **90** while the subscriber is scrolling the tiles of one of the displays **52**, **54**, or **56**.

The preferred program summary panel **90** includes a preview section **92** and a text description section **94**. The preview section **92**, which has a size of 192×144 pixels, can show actual broadcast video data for a current program, or preview media information, including an "on-demand" attract clip or a still graphic image, such as a program title screen or a representative scene of a selected program. In addition, synchronized audio can be played to supplement the still graphic image or video data presented by the preview section **92**. This allows a continuation of the broadcast audio when the subscriber switches from a program channel that delivers a program to the schedule display **50** that presents scheduling information about available programs.

More specifically, for current programs, the preview section **92** provides an opportunity for the subscriber to easily identify and evaluate a selected program. For past and future programs, the preview section **92** can display on-demand attract clips, which may be a more effective mechanism for attracting viewers than text-only descriptions of the programming. In addition, still graphic images can be used if an actual broadcast video signal for a current program or an on-demand attract clip is not available.

The preview section **92** can display an actual broadcast video signal if the current time is consistent with the time slot for the program represented by the selected program tile **66** appearing within the viewing panel **58**. This video display is sized to match the size of the preview section **92**. The actual broadcast video signal is supplied by a tuner, such as the tuner for the set-top converter **32** or the receiving device **34**, and is scaled to fit within the window display of the preview section **92**. The program represented by the selected program tile **66** defines the absolute MSO channel and, in turn, this absolute MSO channel designates the tuning frequency for the tuner.

If the current time is not consistent with the time slot for the selected program tile **66**, then the preview window of the preview section **92** displays an on-demand attract clip or video preview, if one is available, scaled to fit within the preview window. The video data for the on-demand attract clip data is preferably stored within a Tiger video file, which is queued at the beginning of the file and played through to the end of the file. The Tiger video file for the appropriate on-demand attract clip is retrieved in response to a pointer

supplied by the selected program tile. Each Tiger video file is preferably stored at the location of the headend processor **14** and distributed in response to a request output by the subscriber's set-top converter **32**.

If neither a current program broadcast video signal nor an on-demand attract clip is available for the selected program tile **66**, a still graphic image can be scaled and displayed within the preview window of the preview section **92**. Each graphic image is preferably stored at the location of the headend processor **14** within a bitmap file that is linked to associated programming information maintained within the memory storage device **12**. In addition, audio voice-over or background music stored within a .WAV file may be linked to this programming information. Alternatively, the audio voice-over or the background music can be supplied by a Tiger audio stream associated with the programming information. In either case, the selected program tile **66** appearing within the viewing panel **58** has a pointer that points to the corresponding still graphic image, thereby linking the programming information to the appropriate graphic image.

For the preferred schedule display **50**, a transition between preview information supplied by the preview section **92** is indicated by either a fade to a selected color, such as dark gray, and a subsequent fade to the preview image, or a direct fade to the preview image.

The text description section **94**, which has a size of 360×144 pixels, presents detailed information about a selected program represented by the program tile **66** appearing within the viewing panel **58**. This text and/or graphic-based information typically cannot be presented within the smaller frame of a program tile **66** because of the requirement of displaying more than one program tile within the limited available screen dimensions for a conventional display **38**. The text description section **94** can include a program title **96** defining the name of the program and a program description **98** generally describing the nature of the program. In particular, the program title **96** preferably displays the full name in bold typeface of the program associated with the selected program tile **66** appearing within the viewing panel **58**. The program title **96** can be either a simple title naming the series or a compound title naming both a series and the title of a particular episode.

The program description **98** can display the full description of the selected program for the program tile **66** appearing within the viewing panel **58**. This program description **98** is preferably implemented as a text-based field capable of displaying various text attributes, including italic, bold, underline, and different fonts and point sizes.

The text description section **94** also can include one or more information icons, which are graphical images representing particular types of information, such as star ratings, closed captioning, rerun, audience rating, etc. The bottom line of the text description section **94** is preferably used to display such information icons as required to present secondary information. Because some programs may be associated with a large set of information icons, the information icons are preferably ranked in order of priority to insure readability of the text description section **94**. If display space is limited, this priority ranking scheme allows the most significant items of secondary information to be displayed within the text description section **94**.

For the example offered by the schedule display **50** of FIGS. **2–4**, the program title **96** is "NCAA Basketball—Illinois vs. Indiana." and the program description **98** is "Henson's Fighting Illini meet up with Bobby Knight's Hoosier Team in this Big Ten Conference Matchup."

For the preferred schedule display **50**, a transition between preview information supplied by the text description section **94** is indicated by a fade to a selected color, such as light ray, and a subsequent fade to the text-based image.

For the representative example provided by the schedule display **50** of FIGS. **2–4**, the preview section **92** shows a graphic image of a basketball and the logo "NCAA" centered on the basketball. This graphic image is consistent with the text presented within the text description section **94**, specifically "NCAA Basketball—Illinois vs. Indiana. Henson's Fighting Illini meet up with Bobby Knight's Hoosier Team in this Big Ten Conference Matchup."

FIGS. **6–8** illustrate another embodiment for the presentation of programming information, the schedule display **50'**, which includes a modified version of a program display for displaying program-related information. FIG. **6** illustrates the focus frame **60** located proximate to the category display **52**, FIG. **7** illustrates the focus frame **60** located proximate to the subcategory display **54**, and FIG. **8** illustrates the focus frame **60** located proximate to the program display **56'**. Focusing now upon the alternative schedule display **50'** of FIGS. **6–8**, it will be seen that date information for program is not presented by each of the program tiles **66'** of the program display **56'**. Instead, the program display **56'** has been modified to include a date tile **80** containing date information to distinguish programs tiles **66'** that are associated with a first date from program tiles **66'** for a second date.

Data tiles **80** can be added to the program display **56'** because the program tiles **66'** for available programs are typically grouped in chronological order. Date tiles **80** are preferably the same size and shape as the program tiles **66'**, but contain only date-related information. For example, the format for a date tile **80** can be "Wednesday, April 20" to define a date context for the displayed program tiles. Unlike the program tiles **66'**, date tiles **80** cannot be selected by the subscriber and, accordingly, date tiles **80** do not appear within the viewing panel **58**. For example, if the last program for a date is currently selected, and the subscriber scrolls the program tiles **66'** forward through time, the first program of the next date will appear within the viewing panel **58** and the associated date tile **80** will appear as the first tile immediately above the viewing panel **58**.

The program display **56'** also includes a date status indicator **82** to provide additional date context for the program dates and times presented by the date tiles **80**. If a date tile **80** is scrolled off the top of the program display **56'**, then the date status indicator **82** displays the date associated with that particular date tile. For example, the date status indicator **82** for the schedule display **50** of FIG. **6** shows the date information "Tuesday, April 19" because the date tile **80** associated with that date has already scrolled off the top of the program display **56'**. If the subscriber continues to scroll through the program tiles **66'** shown in FIG. **6**, then the date tile for "Wednesday, April 20" will eventually scroll off the top of the program display **56'**, thereby resetting the date of the date status indicator **82** to that particular date.

Each program tile **66'** represents information about a selected program and can display the program title or name, and the channel number. Each program tile **66'** also can include the network name and the network symbol, which is typically implemented as an icon graphically representing the logo of the corresponding channel or network. If display space is available within the limited area of the program tile, then program information of secondary interest to the user can be presented as information icons on the program tiles

66'. Information icons, which are graphical images representing secondary information items, can be used to reduce the amount of text displayed by a program tile, thereby making it easier for the subscriber to locate and read the program titles. Information icons can represent a variety of secondary program-related information, including the items of closed captioning, audience rating, awards, star rating. or reruns status. It will be understood that the use of information icons is an option for the user interface supplied by the program schedule **50'**.

FIG. **9** is a logical flow diagram illustrating the steps of the preferred method for retrieving and displaying programming information. Referring to FIGS. **1–4** and **9**, the method starts at the START step **100** and proceeds to step **102** to select the presentation of the schedule display **50**. The subscriber typically can select the display of the program schedule **50** by instructing the set-top converter **32** or the receiving device **34** to tune to a particular channel associated with the program guide system **10**. By changing from an actual broadcast channel to the channel for the program guide system **10**, the schedule display **50** can be presented by the display **38** for viewing by the subscriber.

In response to selecting the option of the schedule display **50**, the subscriber can select the desired category of programming information by scrolling the category tiles **62** of the category display **52** until the category tile **62** representing the selected category appears within the viewing panel **58**. This preferably resets the subcategory display **54** to display subcategory tiles **64** representing subcategory items associated with the selected category. In turn, the subscriber can select a desired subcategory item in step **106** by scrolling the subcategory tiles **64** of the subcategory display **54** until a subcategory tile **64** representing the selected subcategory appears within the viewing panel **58**. In step **108**, an inquiry is conducted to determine whether a program is available that corresponds to the selected subcategory. If the response is positive, then the "YES" branch is followed to step **110**. In step **110**, the program display **56** is preferably reset to display program tiles **66** representing available program items associated with the selected subcategory. This allows the subscriber to select programming information about a desired program by scrolling the program tiles **66** of the program display **56** until a program tile **66** representing the desired program appears within the viewing panel **58**. In this manner, the subscriber views the selected category, subcategory, and program items within the viewing panel **58** to obtain the desired programming information.

If the response to the inquiry of step **108** is negative, then the "NO" branch is followed to step **112**. In step **112**, the schedule display **50** supplies an indication to the user that a program associated with the selected subcategory is not available. In response, the user can elect to select either a new category or subcategory to obtain a new class of programming information. If the user wishes to change the selected category, the "YES" branch is followed from step **114** to step **104**. Otherwise, the user can change the selected subcategory and the "NO" branch is followed to step **106**.

The process concludes at the END step **116**.

FIG. **10** is a flow chart diagram illustrating the steps of operation for the preferred program display supplied by the program schedule system **10**. Referring now to FIGS. **1–4** and **10**, operation of the program schedule system **10** starts at the START step **120** in response to the user's selection of the display of the program schedule **50**. In step **122**, an inquiry is conducted to determine whether the user has previously used the program schedule system **10** by viewing the schedule display **50**. If the response is positive, then the "YES" branch is followed to step **124** and the category display **52** is set to display the category tile **62** representing the first possible category. For the preferred schedule display **50**, the category tile **62** presented within the viewing panel **58** represents the category which appears first within the possible categories sorted in alphabetical order. In addition, the subcategory display **54** is preferably set to display the subcategory tile **64** representing the associated subcategory of "All." In contrast, if the response in step **122** is negative, then the "NO" branch is followed to step **126** and the settings for the category and subcategory displays **52** and **54** in the previous viewing session are selected.

From either step **124** or step **126**, the process proceeds to step **128** to set the program display **56**. Specifically, the program tile **66** representing the program associated with the selected category and subcategory and having the closest match with the current time and date is selected to appear within the viewing panel **58**. In this manner, each of the displays **52**, **54**, and **56** is set and tiles representing category, subcategory, and program information appear within the viewing panel **58**.

In step **130**, programming information is retrieved and displayed within the text description section **94** of the program summary panel **90**. This programming information can include both a text-based description of the program associated with the selected program tile **66** and information icons for this program.

In step **132**, an inquiry is conducted to determine if the program represented by the selected program tile **66** is a current broadcast. If so, the "YES" branch is followed to step **134** and the set-top converter **32** is tuned to the appropriate program channel to display the broadcast stream within the preview section **92**. In contrast, if the response to the inquiry in step **132** is negative, then the "NO" branch is followed to step **136**. In step **136**, preview media information, such as an on-demand attract clip or a still graphic image, is retrieved from the location of the headend processor **14** based upon the particular program represented by the selected program tile **66**. In step **138**, a determination is made whether a Tiger video file is available for the selected program. If the response to the inquiry in step **138** is positive, the "YES" branch is followed to step **140**. In step **140**, the Tiger video file for the selected program is cued and the Tiger video stream is displayed within the preview section **92**. Alternatively, if the response to this inquiry is negative, then the "NO" branch is followed from step **138** to step **142**. In step **142**, a digitized still graphic image for the selected program is retrieved and displayed within the preview section **92**.

From step **140** or step **142**, the process continues to step **144**, in which the viewer can update the selected program displayed by the schedule display **50** based upon the viewer's interests, as described with respect to the process of FIG. **9**.

In step **146**, an inquiry is conducted to determine whether the display of the program schedule **50** should be discontinued. For example, the program schedule session can be discontinued by changing the channel of the set-top converter **32** to a channel other than the channel for the schedule display **50**. If the response is positive, the "YES" branch is followed to step **148** and the selected category, subcategory, and program-related information are stored. Otherwise, the process continues by returning to step **130**. The process concludes in step **150**, the END step.

In summary, the present invention provides a programming guide system for retrieving and displaying program-

ming information for a subscriber of programming services. The programming information is typically stored at a location which is remote from the subscriber's location and is distributed to the subscriber via a headend processor and a cable distribution network. Each subscriber can then receive the programming information via a set-top converter that is connected to a receiving device, such as a television or a monitor. The monitor supports the display of a schedule display that presents three classes of programming information, including categories, subcategories, and programs. The schedule display includes three displays, a category display, a subcategory display, and a program display. Each display can display an array of tiles representing corresponding programming information. A viewing panel extends along each of the displays for displaying one each of the category, subcategory, and program tiles. In response to a category tile representing a selected category appearing within the viewing panel, the subcategory display displays at least one subcategory tile representing a subcategory associated with the selected category. Likewise, in response to a subcategory tile representing a selected subcategory appearing within the viewing panel, one program display displays at least one program tile representing an available program associated with the selected subcategory. This allows the subscriber to view the selected programming information within the viewing panel of the schedule display.

From the foregoing, it will be appreciated that the present invention indeed fulfills the needs of the prior art described herein above and meets the above-stated objects and advantages. While there has been shown and described the preferred embodiment of the invention, it will be evident to those skilled in the art that various modifications and changes may be made thereto without departing from the spirit and the scope of the invention as set forth in the appended claims and equivalents thereof.

We claim:

1. A method for retrieving and displaying electronic information relating to a category, a subcategory and program scheduling, comprising the steps of:

selecting one of a plurality of categories of said electronic information by scrolling a category display displaying an array of category tiles representing said categories until one of said category tiles representing said selected category appears within a viewing panel;

selecting one of a plurality of subcategories of said electronic information by scrolling a subcategory display displaying an array of subcategory tiles representing said subcategories until one of said subcategory tiles representing said selected subcategory appears within said viewing panel, each of said subcategories being associated with at least one of said categories; and

selecting one of a plurality of programs of said electronic information by scrolling a program display displaying an array of program tiles representing said programs until one of said program tiles representing said selected program appears within said viewing panel, each of said programs being associated with at least one of said subcategories,

wherein said viewing panel extends along at least a portion of said category display, said subcategory display, and said program display to display one each of said category tiles, subcategories tiles, and program tiles.

2. The method recited in claim **1**, wherein each of said subcategories is associated with said selected category, and each of said selected programs is associated with said selected subcategory.

3. The method recited in claim **1**, wherein selecting one of said categories causes said subcategory display to show at least one of said subcategory tiles representing one of said subcategories associated with said selected category, and selecting one of said subcategories display causes said program display to show to at least one of said program tiles representing one of said programs associated with said selected subcategory.

4. The method recited in claim **3**, wherein scrolling said program display moves chronologically through said program tiles representing programs that are associated with said selected subcategory.

5. The method recited in claim **1**, wherein said step of selecting one of said categories comprises:

moving a focus frame along said viewing panel to said category display, said focus frame operative to supply an indication of user control of the display of said category tiles when said focus frame is positioned along said category display;

scrolling in a selected vertical direction said category tiles until said category tile representing said selected category appears within said viewing panel.

6. The method recited in claim **1** wherein said step of selecting one of said subcategories comprises:

moving a focus frame along said viewing panel to said subcategory display, said focus frame operative to supply an indication of user control of the display of said subcategory tiles when said focus frame is positioned along said subcategory display;

scrolling in a selected vertical direction said subcategory tiles until said subcategory tile representing said selected subcategory appears within said viewing panel.

7. The method recited in claim **1**, wherein said step of selecting one of said programs comprises:

moving a focus frame along said viewing panel to said program display, said focus frame operative to supply an indication of user control of the display of said program tiles when said focus frame is positioned along said program display;

scrolling in a selected vertical direction said program tiles until said program tile representing said selected program appears within said viewing panel.

8. The method recited in claim **1**, wherein said array of category tiles and said array of subcategory tiles are maintained in alphabetical order for represented categories and subcategories.

9. The method recited in claim **1**, wherein said array of program tiles is maintained in time-sorted order for represented programs.

10. The method recited in claim **1**, wherein each of said program tiles comprises at least program name, program date and start time, and program channel.

11. The method recited in claim **1**, wherein said program tiles are ordered in time-sorted order for represented programs, and said program display includes a plurality of date tiles representing dates, each of said date tiles separating said program tiles associated with one of said dates from said program tiles associated with another one of said dates.

12. The method of claim **11**, wherein said program display further comprises a date status indicator operative to display one of said dates associated with one of said program tiles appearing within said viewing panel.

13. The method of claim **1**, wherein said category display, said subcategory display, and said program display are

operative to display at any particular interval up to a predetermined number of said category tiles, said subcategory tiles, and said program tiles.

14. A system for displaying electronic information relating to a category, a subcategory and program scheduling, comprising:

a category display for displaying an array of category tiles representing categories of said electronic information;

a subcategory display for displaying an array of subcategory tiles representing subcategories, each of said subcategories associated with at least one of said categories, said subcategory display indicated adjacent to said category display;

a program display for displaying an array of program tiles, each of said programs associated with at least one of said subcategories, said program display located adjacent to said subcategory display; and

a viewing panel extending along a portion of each of said category display, said subcategory display, and said program display for displaying one each of said category tiles, subcategory tiles, and program tiles,

wherein said subcategory display, responsive to one of said category tiles representing a selected category appearing within said viewing panel, displays at least one of said subcategory tiles representing one of said subcategories associated with said selected category, and

said program display, responsive to one of said subcategory tiles representing a selected subcategory appearing within said viewing panel, displays at least one of said program tiles representing an available one of said programs associated with said selected subcategory.

15. The system recited in claim 14, wherein said array of category tiles and said array of subcategory tiles are maintained in alphabetical order for represented categories and subcategories.

16. The system recited in claim 14, wherein said array of program tiles is maintained in time-sorted order for represented programs.

17. The system recited in claim 14, wherein each of said program tiles comprises at least program name, program date and start time, and program channel.

18. The system recited in claim 14, wherein said program tiles are ordered in time-sorted order for represented programs, and said program display includes a plurality of date tiles representing dates, each of said date tiles separating said program tiles associated with one of said dates from said program tiles associated with another one of said dates.

19. The system of claim 18, wherein said program display further comprises a date status indicator operative to display one of said dates associated with said program tile appearing within said viewing panel.

20. The system of claim 14, wherein said category display, said subcategory display, and said program display are operative to respectively display up to a predetermined number of said category tiles, said subcategory tiles, and said program tiles.

21. The system of claim 14, wherein said category tiles are stored within a database and are retrievable to support the display of said category tiles by said category display.

22. The system of claim 21, wherein said subcategory tiles are stored within said database, and at least one of said subcategory tiles representing one of said subcategories associated with said selected category is retrieved from said database in response to one of said category tiles representing said selected category appearing within said viewing panel.

23. The system of claim 22, wherein said program tiles are stored within said database, and at least one of said program tiles representing one of said programs associated with said selected subcategory is retrieved from said database in response to one of said subcategory tiles representing said selected subcategory appearing within said viewing panel.

24. A method for selecting and displaying electronic information relating to a category, a subcategory and program scheduling, comprising the steps of:

selecting one of a plurality of categories of said electronic information by scrolling a category display displaying an array of category tiles representing said categories until one of said category tiles representing said selected category appears within a viewing panel;

selecting one of a plurality of subcategories of said electronic information, each of said subcategories, being associated with said selected category, by scrolling a subcategory display displaying an array of subcategory tiles representing said subcategories until one of said subcategory tiles representing said selected subcategory appears within said viewing panel; and

selecting one of a plurality of programs of said electronic information, each of said programs being associated with said selected subcategory, by scrolling a program display displaying an array of program tiles representing said programs until one of said program tiles representing said selected program appears within said viewing panel,

wherein said viewing panel extends along at least a portion of said category display, subcategory display, and program display and supplies a highlighted display one each of said category tiles, said subcategory tiles, and said program tiles appearing within said viewing panel.

25. The method recited in claim 24, wherein said array of category tiles and said array of subcategory tiles are maintained in alphabetical order for represented categories and subcategories, and said array of program tiles is maintained in time-sorted order for represented programs.

26. The method recited in claim 24, wherein said program tiles are ordered in time-sorted order for represented programs, and said program display includes a plurality of date tiles representing dates, each of said date tiles separating said program tiles associated with one of said dates from said program tiles associated with a another one of said dates.

27. The method of claim 24, wherein said program display further comprises a date status indicator operative to display one of said dates associated with said program file appearing within said viewing panel.

28. In a computer system having a user interface presented on a display device and responsive to an input device, a method for presenting on said display device electronic information relating to a category, a subcategory and program scheduling, comprising the steps of:

displaying on said display device a category display comprising a plurality of category tiles representing categories of said electronic information;

displaying on said display device a subcategory display comprising a plurality of subcategory tiles representing subcategories, each of said subcategories associated with at least one of said categories, said subcategory display located adjacent to said category display;

displaying on said display device a program display for displaying comprising a plurality of program tiles representing programs, each of said programs associated

with at least one of said subcategories, said program display located adjacent to said subcategory display;

displaying on said display device a viewing panel extending along a portion of each of said category display, said subcategory display, and said program display for displaying one each of said category tiles, subcategory tiles, and program tiles; and

displaying on said display device a focus frame, responsive to commands from the input device, movable along said viewing panel and proximate to one of said category display, said subcategory display, and said program display, for enabling control of the presentation of one of said category tiles, subcategory tiles, and program tiles.

29. The method of claim **28** further comprising the step of determining if one of said category tiles representing a selected category appears within said viewing panel and, if so, then displaying within said subcategory display one of said subcategory tiles representing one of said subcategories associated with said selected category.

30. The method of claim **28** further comprising the step of determining if one of said subcategory tiles representing a selected subcategory appears within said viewing panel and, if so, then displaying within said program display one of said program tiles representing an available one of said programs associated with said selected subcategory.

31. The method of claim **30**, wherein said category tiles, subcategory tiles, and program tiles are stored within a database connected to said computer system, and said step of displaying said category display comprises retrieving said category tiles from said database and presenting one of said retrieved category tiles within said category display.

32. The method of claim **31**, wherein said step of displaying said subcategory display comprises (1) retrieving said subcategory tiles representing one of said subcategories associated with said selected category from said database in response to one of said category tiles representing said selected category appearing within said viewing panel, and (2) presenting one of said retrieved subcategory tiles within said subcategory display.

33. The system of claim **32**, wherein said step of displaying said program display comprises (1) retrieving said program tiles representing one of said programs associated with said selected subcategory in response to one of said subcategory tiles representing said selected subcategory appearing within said viewing panel, and (2) presenting one of said retrieved program tiles within said program display.

34. The method recited in claim **33**, wherein each of said program tiles comprises at least program name, program date and start time, and program channel.

35. The method recited in claim **28** wherein said category display is responsive to commands from said input device when said focus frame is placed proximate to said category display, and further comprising the step of receiving a first command to move said focus frame along said viewing panel and, upon positioning said focus frame proximate to said category display, receiving a second command to scroll said category tiles of said category display in alphabetical order.

36. The method recited in claim **28** wherein said subcategory display is responsive to commands from said input device when said focus frame is placed proximate to said subcategory display, and further comprising the steps of receiving a first command to move said focus frame along said viewing panel and, upon positioning said focus frame proximate to said subcategory display, receiving a second command to scroll said subcategory tiles of said subcategory display in alphabetical order.

37. The method recited in claim **28** wherein said program display is responsive to commands from said input device when said focus frame is placed proximate to said program display, and further comprising the steps of receiving a first command to move said focus frame along said viewing panel and, upon positioning said focus frame proximate to said program display, receiving a second command to scroll said program tiles of said program display in chronological order.

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